UTMJ

University of Toronto Medical Journal

Volume 77, Number 1/December, 1999

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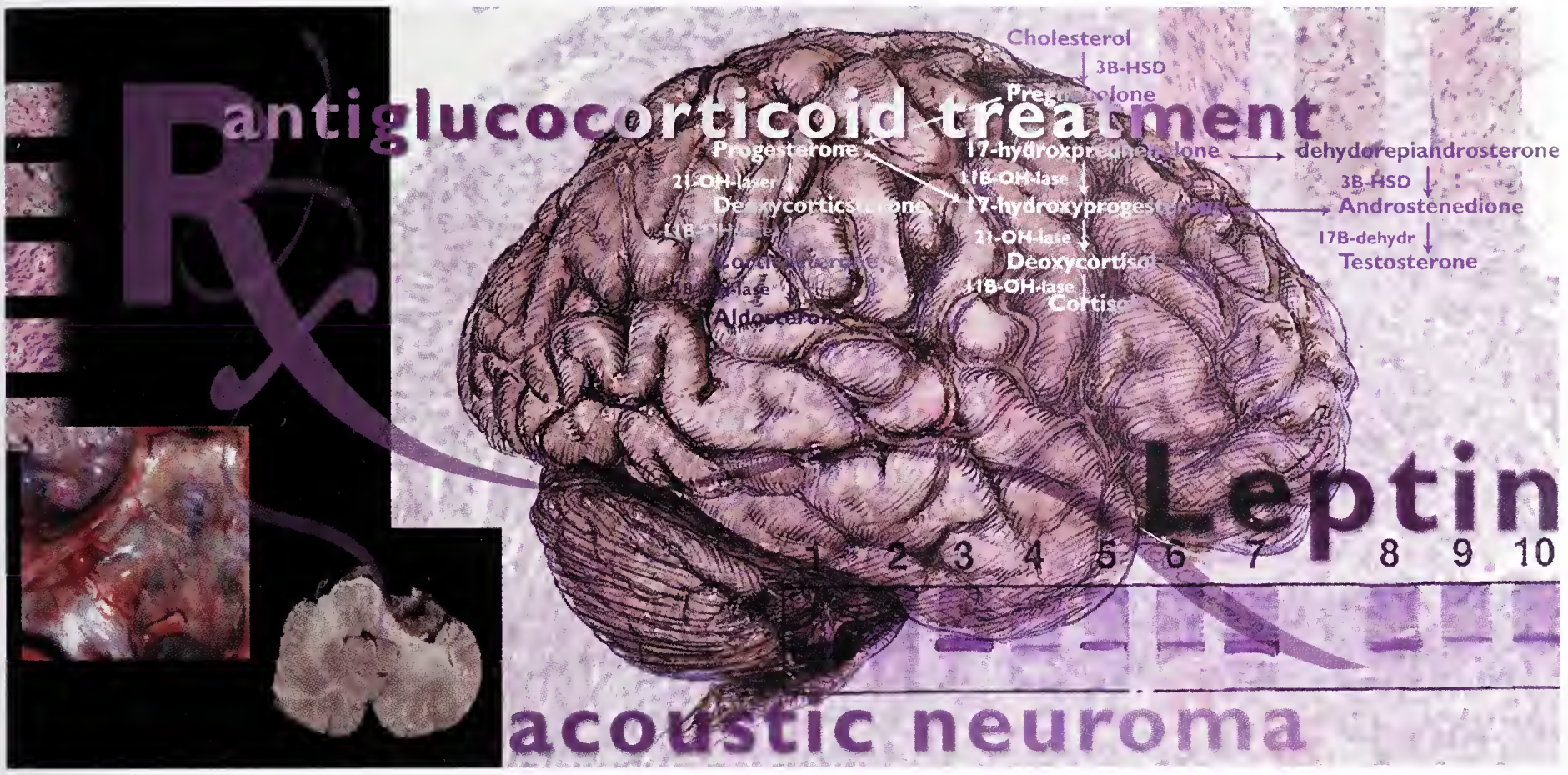

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A Letter to Our Patrons

Perusing through back-issues of the *UTMJ*, one comes across the most important page of the *Journal*, the list of patrons. The names on this page mean much more to us than the generous monetary contributions made by these individuals and institutions. Rather, this page serves to remind us that our patrons are keenly aware of the value and importance of maintaining Canada's oldest student-run publication. How can we be so sure that our patrons feel this way? Because, for the most part, the names on this page have not changed. This support, although greatly appreciated, has been mostly quiet in nature. In order to understand why this was the case, we decided to meet many of you this past summer.

Many of our patrons were very receptive to our scheduled meetings. Praise, tributes, and compliments on the success of the *Journal* were made. It was through our one-on-one meetings, however, that we discovered that the mandates of the *Journal* might have been misinterpreted over the past years. "Why should I subscribe to the *UTMJ* when there is a plethora of journals out there?" Or, "Why should I encourage my students/residents to submit an article when it can go somewhere else?" were common questions we were asked.

Our answer to these questions required some introspection and examination of the founding editor's, Dr. Benjamin Johnstone (2T4), two goals: 1) to encourage writing and preparing papers among medical students; and, 2) to keep students abreast with recent advances appearing in the current literature. Back in 1922, it might have been a realistic goal to make the *Journal* a central, one-stop resource to read about recent innovations in science and medicine. As the end of this century draws to a close, we would challenge any medical journal to uphold this goal! Thus, we felt it was time to amend the founding goals of the *Journal*, while upholding their spirit. Our vision for the *UTMJ* 1999-2000:

> In keeping with Johnstone's first objective, the *Journal* serves to provide students with a foray into the world of biomedical publishing; to provide a forum for original articles, review articles, case reports, and general interest articles about the science and humanities of medicine.
>
> Create a living laboratory for medical scholarship in and around the *Journal*; to provide firsthand experience in all aspects of biomedical editing, review, and publishing that is managed and upheld completely by students in the Faculty of Medicine.
>
> Develop a useful resource for teachers; to provide a forum in which teacher and student can present their ideas and, in doing so, promote a unique learning experience.

We, and our staff, strongly believe that no other medical journal can match this vision with the same standard of excellence that the *Journal* has consistently showcased for the past 76 years.

This 77th year of publication promises to build upon the *Journal's* legacy. Towards this end, we have assembled the largest staff in the *Journal's* history and have developed a number of new series, reflecting the interests of current medical students. Furthermore, in an attempt to increase our readership and make communication with the *Journal* easier, we have completely revamped our website at www.utmj.org. Lastly, in order to encourage submissions, we have established the *UTMJ* Editors' $1000 Award for the most deserving submission of the 77th volume.

Finally, after completing our tour of meetings this past summer, it became clear to us that a number of patrons subscribe to the *Journal* as a means of supporting their *alma mater*. While we are indebted to this support, we challenge you as a conscientious patron and educator to expand this degree of support. Become a loud supporter of the *UTMJ*; encourage your colleagues and peers to subscribe; encourage your students to submit; and be proud that you are supporting a unique vehicle - a distinguished University of Toronto tradition - that gives students the opportunity to synthesize and share their views with fellow students, colleagues, teachers, mentors, and clinicians.

Raymond H. Kim
Peter K. Stotland
Editors-in-Chief

Preface from the Editors

As this is the last issue of the century, we found it fitting to focus on the last scientific frontier: the neurosciences. Ur *et al.* have thoroughly examined the literature and ask: "Is leptin all in the mind?"; Kongkham writes a thorough account about the diagnosis and treatment of acoustic neuromas; and Lewis examines the role of antiglucocorticoid treatment in depression.

Questions surrounding public policy, ethics, and the use of clinical trials are relevant in medicine today. Compensation and physician benefits are likely to be an emerging issue of discussion within the next century and Leitch and Walker give an informative overview of this subject. Dickens discusses the time-honoured duty of physician-patient confidentiality in the new series, Law, Ethics in Medicine, and Weil writes an overview of basic statistical indices employed in all clinical trials in the new series, Evidence-Based Medicine.

We are proud to continue our well-received clinical sections: Clinicopathological Correlation presents findings of edema, Morning Report is a pain in the chest, and Quick Diagnosis takes us into the O.R. In addition, we start a new series, Back to Basics, and this issue reviews the electrocardiogram. As always, Technology Review and Book Reviews offer insightful opinions for the reader.

We encourage comments and queries about anything we publish. Inquiries may be directed to the Editors at **editors.utmj@utoronto.ca** or visit us online at **www.utmj.org**.

We hope you enjoy Volume 77, Number 1.

R.H.K. and P.K.S.

Leptin and Obesity: Is it All in the Mind?

Ehud Ur, M.B., B.S.*‡, Barbara Morash, Ph.D.‡, Cindee Leopold, B.Sc.§, and Michael Wilkinson, Ph.D.*‡

Abstract

Obesity, defined as an increase in body fat, is a growing problem in Western societies. In Canada over 30% of the population is obese. Obesity is associated with increases in hypertension (high blood pressure), type 2 diabetes, hyperlipidemia (high cholesterol), ischemic heart disease, and a number of other conditions. Factors that regulate food intake and energy expenditure are poorly understood. Leptin is a novel protein, produced by fat cells, that acts on the brain in order to reduce food intake and increase energy expenditure. Until recently, leptin was thought to be produced only by fat cells. We have discovered that the brain, and in particular the hypothalamus, which is the part of the brain that controls appetite and weight, makes leptin itself. Most human obesity appears to involve the brain ignoring the high levels of leptin in the blood, and we believe that this comes about because the key regulator in the hypothalamus is locally-derived leptin. Our findings may have important implications for an understanding of the causes of obesity and may help improve treatments for this metabolic disease.

Introduction

Obesity is a growing problem in North America and in Western Europe. In Canada over 30% of the population are obese.[1] Obesity is associated with increases in hypertension, type 2 diabetes, hyperlipidemia, ischemic heart disease and a number of other conditions.[2] Obesity is a consequence of an increase in caloric intake compared to energy expenditure. However, its origins are poorly understood. Heritability has been estimated to be around 30%,[3] and a number of rodent models exist for genetic obesity. The genes responsible for several of these genotypes have been cloned[4, 5, 6] and a novel physiological system based on the hormone leptin, and its receptors, has been identified. Human homologues are known for some of these mutations.[7, 8]

Since its discovery in 1994, studies on leptin have generated over 2000 Medline citations and several reviews of this expanding literature are already available.[9, 10, 11] The native peptide and several analogues are undergoing phase II therapeutic efficacy trials in subjects with obesity and type 2 diabetes.[12] Leptin is secreted by adipocytes in response to feeding[13] and circulates as both free and bound forms.[14, 15] The free, presumably bioactive, form enters the brain and binds to specific receptors (OB-R; see below). Leptin plays a crucial role in the regulation of body fat levels by co-ordinating metabolism, feeding behaviour, energy balance and neuroendocrine response via actions mainly in the hypothalamus. Metabolic factors which influence leptin secretion include adiposity,[16] fasting[17] and caloric loading.[18] There is a diurnal rhythm of plasma leptin levels entrained to meal timing.[19]

There are also important hormonal regulatory influences on leptin production. Estradiol regulates leptin gene expression in rat adipocytes.[20, 21] Serum leptin is reduced by testosterone in women whereas estrogen increases it in men and women.[22, 23] Glucocorticoids stimulate leptin synthesis peripherally[24] but may contribute to leptin resistance and obesity centrally.[25, 26, 27] Several recent reviews provide further details of leptin gene regulation.[28, 12, 29]

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Brain Leptin Receptors

The effects of leptin in the hypothalamus are mediated by specific receptors as well as a complex neurochemical signalling system that includes melanocortins, cocaine and amphetamine-related transcript (CART), corticotropin releasing factor (CRF), galanin, neurotensin, neuropeptide Y (NPY), hypocretins/orexins and steroid hormones.[30, 31, 32, 33, 34, 10, 35]

Leptin receptors exist in the form of at least five splice variants; a single long form with cell signaling characteristics and four shorter forms, which may serve to transport the peptide across the blood-brain barrier (BBB)[36, 37, 38] or as a circulating binding protein.[38a] The rodent brain has been mapped with specific probes for the long (OB-R_b) and short (OB-R_s) mRNA splice variants.[39, 40, 9] OB-R_b, which is absent in the obese db/db mouse, mediates the satiety effects of leptin whereas OB-R_s is localized to the choroid plexus and brain microvessels. The *fa/fa* (Zucker) rat mutation occurs in the extracellular domain of the OB-R and results in defective transport from the periphery.[41] A soluble human leptin receptor has also been described.[42]

Elmquist *et al.* report an extensive distribution of OB-R_b mRNA in the rat hypothalamus.[9] Other labelled sites, including the thalamus, cerebellum and substantia nigra, imply that leptin may act on sensory and motor systems perhaps unrelated to body weight regulation. Studies in the human brain also suggest a wide distribution of OB-R immunoreactivity, including hypothalamus, cerebellum and the nucleus basalis of Meynert.[43] This latter observation is intriguing, given that patients with Alzheimer's disease have low body weight despite adequate food intake.[44]

Why are Leptin Receptors Widely Distributed in Brain?

Most studies on the effects of leptin in the brain have been performed in the hypothalamus. Some, but not all, of the hypothalamus is located outside of the blood brain barrier (BBB). Since leptin is a large peptide (16 kDa) it is unlikely to penetrate the BBB and it has been argued that leptin enters the brain parenchyma via a specific transport system located in microvessels,[45, 37] or is transported into the intrathecal space.[46] However, attempts to localize peripherally injected [^{125}I] – leptin failed to show central labelling except at the choroid plexus and the arcuate-median eminence region of the hypothalamus.[47, 48, 49] These data indicate that OB-R located at sites such as hippocampus, substantia nigra and cerebellum, are unlikely to be accessible to circulating leptin. This is consistent with experiments that showed entry of large molecules into brain parenchyma only occurs at the circumventricular regions such as median eminence.[50, 51] Even at these sites peptides may well breach the BBB, but penetrate only a short distance into the brain parenchyma (i.e. from median eminence to arcuate nucleus). A similar conclusion was reached by Herkenham *et al.*[52] in a detailed study of c-fos expression following peripheral injection of IL-1 (see also Elmquist *et al.*[53]). In addition, Sinha *et al.* have suggested that leptin circulates in the form of a leptin-binding protein complex which is even less likely to enter the brain.[54] Indeed in rhesus monkeys, leptin reduces food intake only when administered centrally, suggesting that increases in circulating leptin within the physiological range may not be sufficient to acutely regulate food intake.[54, 55] The counter argument, that a specific transport system for leptin may be located in microvessels and choroid plexus,[45, 37] remains unproven.

Nevertheless, even if transport of leptin into the brain does exist, it does not explain why peripheral injection of high specific activity [^{125}I]- leptin fails to label brain regions outside the hypothalamus.[49] It is conceivable that the labelling of leptin with [^{125}I] might compromise binding and transport of the leptin molecule, though this is unlikely in view of the binding experiments reported by Uotani *et al.*[38] Radioiodinated leptin labelled both long-and short-form (OB-R_b and OB-R_s, respectively) receptors stably expressed in Chinese hamster ovary cells. These receptors had K_d values in the nanomolar range and were able to internalize [^{125}I]-leptin via coated pits, confirming that [^{125}I] – leptin binds normally to its cognate receptor. The authors also observed that the short form receptors (OB-R_s) were more efficient in mediating rapid internalization and degradation of the [^{125}I] leptin than were the long form (OB-R_b) receptors. The data suggest that OB-R_s located in brain microvessels do not transport intact leptin into the brain, but rather ensure that the hormone is degraded before this occurs. Such an 'enzymatic' or 'metabolic' blood-brain barrier has been postulated for neuroactive peptides.[56, 57] OB-R in microvessels could also be related to leptin's action as an angiogenic factor.[58, 59]

In summary, the available evidence supports our hypothesis that peripherally-derived leptin is not the ligand for those leptin receptors located in extra-hypothalamic brain regions such as cerebellum and central cortex. *This leads to the additional hypothesis that leptin, or a leptin-like molecule, biosynthesized in the brain, is the ligand for non-hypothalamic OB-R.* An analogous case has been made for a putative role for insulin in brain.[60, 61] However, in

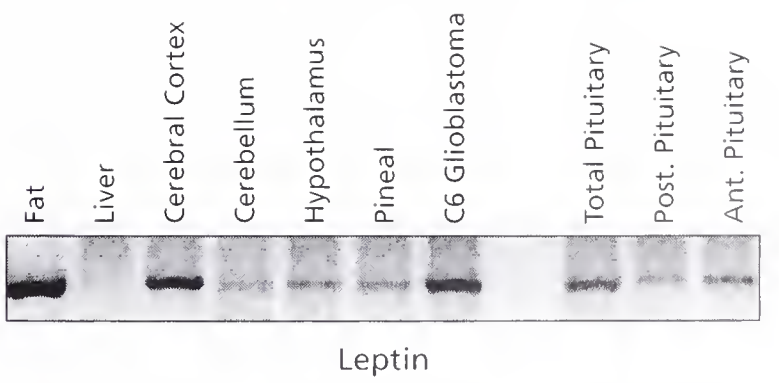

Figure 1. Detection of leptin mRNA in neuronal and peripheral tissues by RT-PCR. *Total RNA was reverse transcribed and PCR-amplified (40 cycles) using primers spanning exons 2 and 3 of the leptin cDNA. A product of the expected size (217bp) was detected in various rat tissues, as shown. No PCR product was detected in liver (lane 2) and in the 'no RT' tubes in lane 8 (modified from Morash et al [62]).*

the case of leptin the hypothesis is of far greater significance since the hypothalamus is considered to be the principal target for leptin of peripheral (adipocyte) origin.

Does the Brain Express the Leptin Gene?

The cloning of the leptin gene[4] stimulated intensive studies on the signaling pathway that links adipose tissue and the hypothalamus. Until recently it was accepted that adipose tissue represented the only source of leptin. However there is now evidence for leptin gene expression in placenta, gastric epithelium, skeletal muscle, breast tissue and adrenal gland.[62, 63, 64, 65, 66]

To establish whether leptin mRNA was expressed in the rat brain, we used reverse transcriptase polymerase chain reaction (RT-PCR) with intron spanning primers directed at a 217 bp region spanning exons 2 and 3 of the leptin transcript. A product of the expected size (217 bp) was detected in the following rat tissues: fat, cerebral cortex, cerebellum, hypothalamus, pineal gland, C6 glioblastoma cells, whole pituitary gland, posterior pituitary and anterior pituitary (Figure 1), indicating that these tissues express leptin mRNA. Leptin mRNA was undetectable in liver and in hippocampus under the same conditions. Sequence analysis of the 217 bp amplicon from fat and hypothalamus confirmed 100% homology with the corresponding region of the published sequence for leptin cDNA. These observations differ from those previously reported in

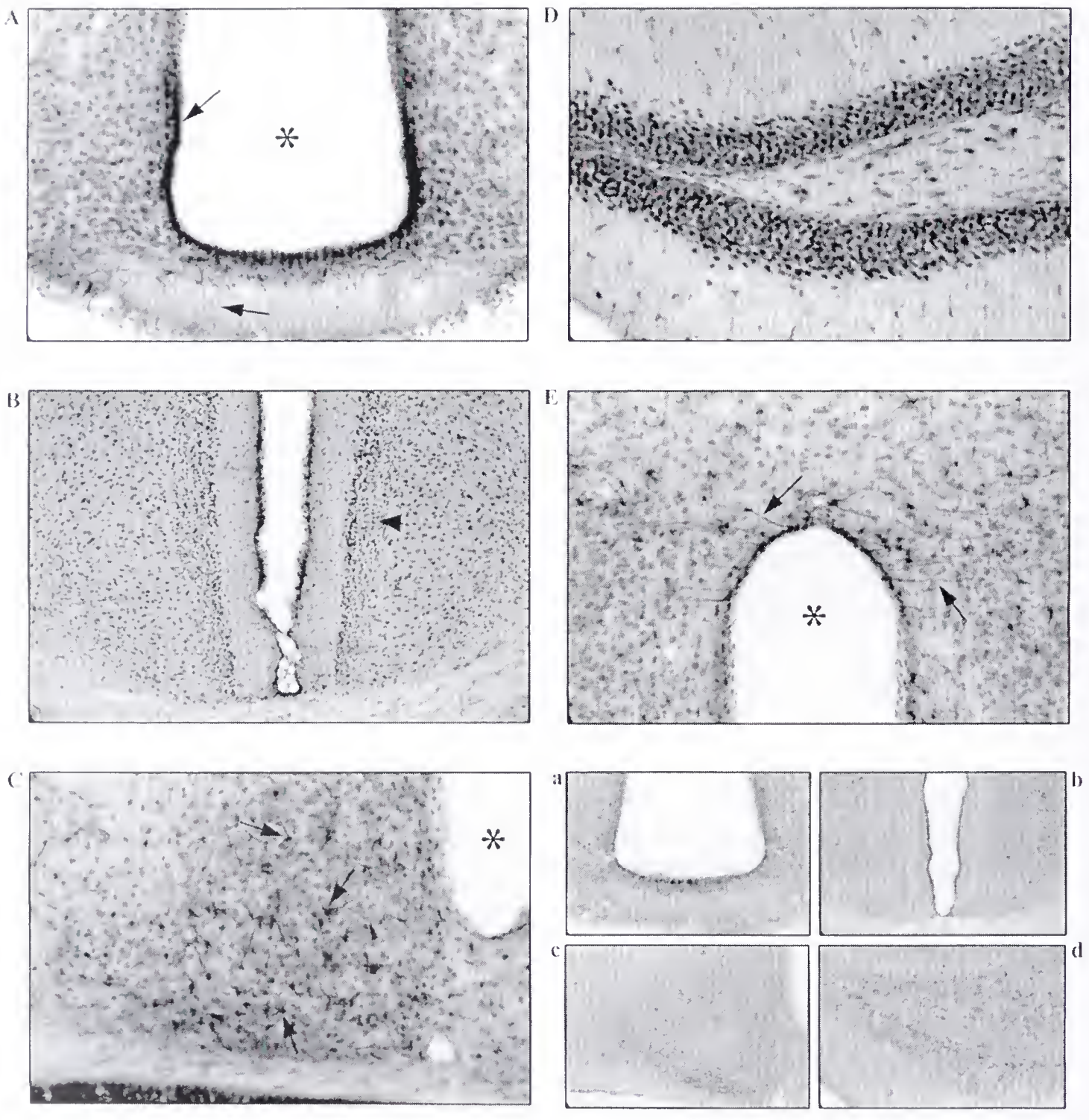

Figure 2. Immunohistochemical detection of leptin in mouse brain. *Coronal sections from fixed brain of adult female mice stained for leptin immunoreactivity using a polyclonal antibody (Santa Cruz, Y20; 1:5000). Panel (A) shows leptin-ir in ependymal cells and tanycytes of the arcuate-median eminence region, panel (B) illustrates leptin-immunoreactivity (leptin-ir) in laminae 2/3 of the ventral retrosplenial cortex; panel (C) shows multipolar cells located in the suprachiasmatic nucleus (SCN), panel (D) illustrates dense nuclear staining in granule cells of dentate gyrus; panel (E) indicates tanycyte-like staining in dorsal hypothalamus. Control sections in panels a) - d) show that immunolabeling was abolished in all regions by pre-adsorbing the primary antibody with the immunizing peptide*

** = third ventricle. Magnifications are x 312, A, C, D, E and a, c, d, x 125, B and b*

the literature.[4] Possible explanations for this include our use of more input RNA for cDNA synthesis, higher cycle numbers and different primers combined with robust optimization of the PCR reaction conditions. A significant difference between our work and that of Zhang *et al.*[4] is their use of mouse tissues. We obtained only a weak signal for the 217 bp product, even in mouse fat (40 cycles).

It could be argued that detection of leptin gene expression by RT-PCR is of doubtful physiological relevance, and merely reflects contamination of brain tissue with adipocytes. We think this is unlikely in view of our inability to detect expression in liver, where adipocyte contamination is much more likely than in brain. In addition, we have observed strong signals for leptin mRNA expression in C6 glioblastoma[67] and pituitary RC-4B/C cells grown in culture (unpublished observations).

Localization of Leptin Protein Immunoreactivity in Mouse Brain

The detection of leptin mRNA expression in brain tissue prompted us to determine the distribution of leptin-immunoreactivity (leptin-ir) in fixed brain sections. Using a polyclonal antibody raised against a peptide sequence at the N-terminus of human leptin (amino acids 16-34; Santa Cruz Biotech # Y-20) we observed intense staining for leptin-like-immunoreactivity (leptin-ir) in rat brain[67] and in mouse and hamster brain. Figure 2 illustrates the localization of leptin-ir in the mouse arcuate nucleus (A), cerebral cortex (retrosplenial; B), the suprachiasmatic nucleus (SCN) (C), hippocampus/dentate gyrus (D) and some tanycyte-like cells in the dorsal hypothalamus (E). Staining was abolished by either omitting the primary antibody from the staining procedure or by pre-adsorbing the primary with the immunizing peptide (panels a-d). With the exception of the hippocampus, leptin-ir is detectable in those brain regions where leptin mRNA was found by RT-PCR. The staining in hippocampus might represent leptin released from afferent neurons.

The immunocytochemical data implies, but does not prove, that leptin is made in the brain. On the other hand, the staining of ependymal cells (Figure 2A) and tanycyte-like cells (Figure 2E) suggests the possibility of uptake of leptin from the cerebrospinal fluid. In these cells, and those in the SCN, the immunoreactivity is clearly cytoplasmic whereas elsewhere (i.e. arcuate nucleus, hippocampus, cortex) it is nuclear. A recent report by Bergeron and Prosser[67a] implicates leptin in the modulation of circadian timing in SCN *in vitro*. Nuclear localization of leptin has not been reported. However, OB-R is a member of the class I cytokine receptor family for which nuclear localization has been described.[67b]

Why is Leptin Made in the Brain?

An important goal would be to determine the type of cell that produces this molecule (glia; neurons). Could it behave as a neurotransmitter/modulator following release from neuron terminals or as some type of glial signalling factor? Figure 3 illustrates specific leptin-ir in C6 glioblastoma cells and in a pituitary cell line (RC-4BC; ATCC # CRL-1903), suggesting that non-neuronal cells can produce leptin and that glia may be one source of brain leptin. Evidence for a role as a neurotransmitter can be gleaned from several reports. A rapid, non-genomic effect of leptin was seen in hypothalamic slice preparations *in vitro*.[68, 69, 70] Sub-nanomolar concentrations of leptin were rapidly and reversibly inhibitory on hypothalamic neurons. A slower, hyperpolarizing effect was also reported in hypothalamic glucose-sensitive neurons from lean rats,[71] but not in tissue from Zucker rats, i.e. rats in which OB-R_b are non-functional. Depolarizing effects of leptin have been identified in neurons of the hypothalamic paraventricular nucleus.[69]

Little work of this type has been done on extra-hypothalamic regions, which also possess high levels of leptin receptors. Lee and Morris[72] observed an inhibitory effect of leptin on depolarization-induced NPY release from cerebral cortex and medulla oblongata. Very low concentrations of leptin (10-14 and 10-12 M) facilitated induction of long term potentiation

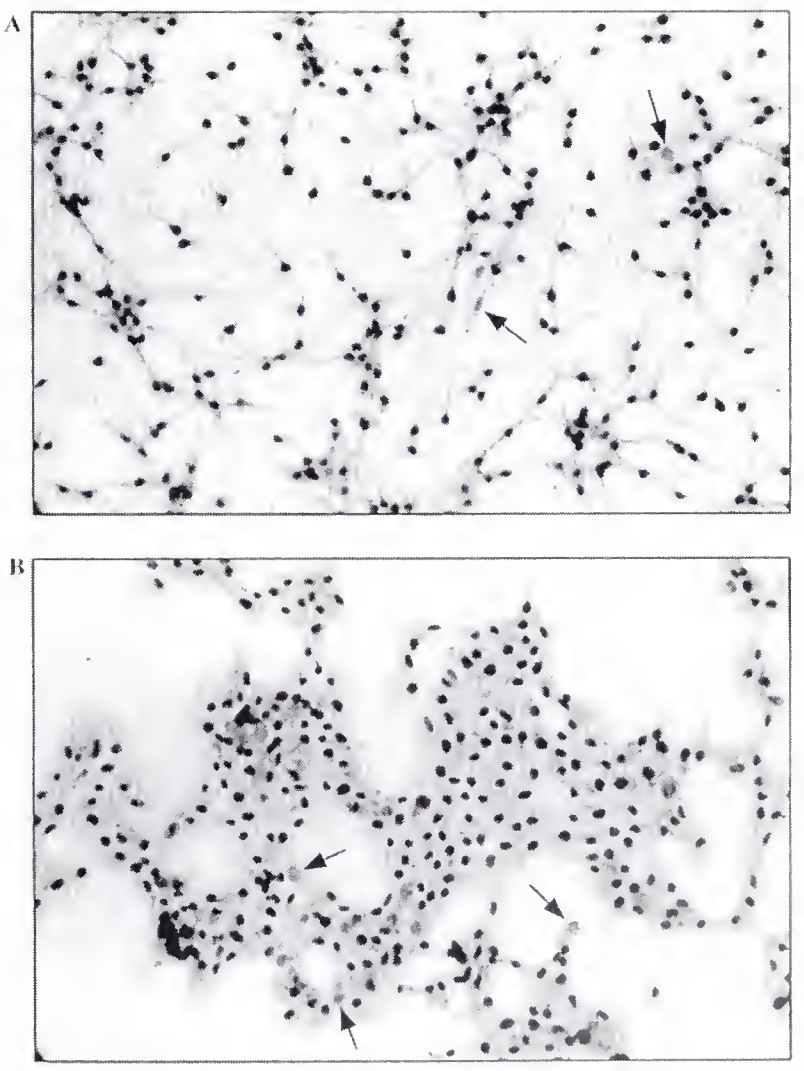

Figure 3. Immunohistochemical detection of nuclear leptin-ir in C6 glioblastoma (A) and in pituitary RC-4BC tumour cells (B). *Note the dense nuclear staining in both cell types and that some nuclei (arrows) are unstained. The C6 cells were cultured in the presence of dibutyryl cAMP (1mM) which greatly reduced the number of unstained cells. Omission of the primary antibody or pre-adsorption of the primary with the immunizing peptide completely eliminated nuclear staining (not shown). Scale bar is 100 µm.*

LTP in rat hippocampal slices.[71] Both these studies indicate that OB-R in non-hypothalamic areas is able to regulate neural activity. More importantly, the effect of leptin on LTP implicates leptin in synaptic events apparently unrelated to food intake and body weight control.

Recent studies indicate that leptin regulates the expression of neuronal and glial proteins.[74, 75] Treatment of ob/ob mice, which lack leptin, with exogenous leptin increases brain size and total brain DNA.[74] A more detailed examination of the effects of leptin replacement revealed a restoration of levels of growth associated protein, syntaxin-1 and synaptosomal associated protein-25.[75] Note that these changes were not confined to hypothalamus but were also seen in neocortex. The data are suggestive of an important role for leptin in brain development. It is noteworthy that Ahima *et al.*[75] also demonstrated the occurrence of neurodegeneration in frontal cortex and hippocampus of untreated ob/ob and db/db mice as compared to wild-type controls, though this was not corrected by treatment with peripherally administered leptin. Our findings that leptin gene expression and leptin protein are detectable in brain strengthen the suggestion that leptin could be an important factor in brain development.[75, 74]

Summary

We have summarized the evidence that leptin gene expression occurs in the brain and that leptin may act as a neurotransmitter/neuromodulator and as a trophic influence in the developing brain. Others have suggested such a possibility. For example, Wiesner *et al.*[76] observed higher levels of leptin in human venous plasma exiting the brain compared to arterial levels. They hypothesized that the brain is a source of leptin. Our data confirm that this is correct. Two other groups have reported the presence of leptin-ir in the hypothalamus of normal and diabetic rats[77] and in sheep.[78] In contrast to our method, they used a different antibody and rats were treated with intraventricular colchicine 48 hours prior to perfusion. Nevertheless cytoplasmic leptin-ir was detectable in hypothalamus and brain stem and hypothalamic leptin-ir was greatly reduced in streptozotocin-induced diabetic rats. These data support our evidence that the leptin gene is expressed in brain tissue. In a recent editorial article, Reichlin also speculated that leptin could be a secretion of the brain. An important issue concerning the expression of leptin in the brain is whether leptin mRNA is detectable in species other than rat. This is necessary to establish a significant role for leptin in brain function. A preliminary RT-PCR analysis revealed that leptin mRNA was detectable in two human pituitary adenomas.[67] We suggest that the prevailing paradigm of leptin as an adipostatic signal from fat to brain is too restrictive and that this hormone performs a pleiotropic role in brain function.

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Acoustic Neuroma: Etiology, Presentation, and Treatment

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Abstract

Acoustic neuromas (vestibular schwannomas) are common, benign tumours of the posterior cranial fossa, arising from the neurilemmal sheath of the vestibulocochlear nerve. The signs and symptoms associated with these tumours are defined by the proximity of the neoplasm to other structures in the cerebellopontine angle. Advances in neurological imaging now permit earlier diagnosis of acoustic neuromas. Surgical innovations such as the intraoperative microscope, cranial nerve monitoring, improvements in microsurgical methodology, and advances in radiotherapy have reduced the morbidity and mortality associated with the treatment of these tumours. This review provides a description of the clinical neuroanatomy of acoustic neuromas and the current treatment strategies available.

Introduction

Acoustic neuromas are benign Schwann cell tumours that arise from the vestibulocochlear nerve (CN VIII) in the posterior cranial fossa. These neoplasms account for approximately 10% of all primary intracranial tumours and are the most common tumour of the cerebellopontine angle (80%), with an incidence of approximately 1 per 100 000.[1-5] Although acoustic neuromas most often occur unilaterally (> 95%) and produce an onset of symptomatology during middle age, bilateral tumours occur in approximately 5% of patients and are pathognomonic for neurofibromatosis type-2 (NF-2).[6-7] Acoustic tumours frequently arise from the superior division of the vestibular portion of CN VIII, proximal to the porous acousticus, in a region of the neurilemmal sheath known as the Obersteiner-Redlich zone (the junction between central and peripheral myelin).[8] Although the rate of tumour expansion is variable (between 1-10 mm per year), the majority of acoustic neuromas grow approximately 1-2 mm annually.[7,8]

Genetics

Deletion of the *NF-2* tumour suppressor gene on the long arm of chromosome 22 is thought to contribute to the initiation of acoustic tumour development.[7-9] This deletion may arise as a somatic or germline mutation, the origin of which predisposes the individual to the development of unilateral or bilateral tumours, respectively. Although mutation of the *NF-2* gene is thought to be the early genetic event that initiates tumourigenesis, neoplastic growth appears to depend upon additional mitogens such as nerve growth factor (NGF), platelet-derived growth factor (PDGF), basic fibroblast growth factor (bFGF), and transforming growth factor beta 1 (TGF - β1).[7, 9-11] Curiously, the known tumour suppresser genes *p53*, *adenomatous polyposis coli* (APC), and *NF-1* do not appear to be important in the development of acoustic tumours.[12]

Signs and Symptoms

The size of the acoustic neuroma usually determines its symptomatology, as growing tumours can compress adjacent cranial nerves (CN) as well as the brainstem and cerebellum (Table 1).[13] In particular, the acoustic neuroma may impinge on the contents of the internal auditory canal, including CN VII, CN VIII and the internal auditory artery.[14] The majority of tumours will produce some form of otologic dysfunction by the time of diagnosis, with the most common symptoms experienced early in this disease being hearing loss, tinnitus, and dysequilibrium (all related to compression of CN VIII).[1, 14-18]

Progressive, unilateral hearing loss occurs almost invariably (~ 98%) in patients with acoustic tumours and commonly man-

Table 1
Significant Surgical Anatomy for Acoustic Neuromas, Organized by Cisterns

CISTERN	LOCATION	CN	ARTERIAL STRUCTURES	SIGNIFICANT VENOUS STRUCTURES
Cerebello-medullary	Lateral to brainstem, caudal to pontomedullary sulcus	IX, X, XI	Vertebral arteries PICA	
Cerebellopontine	Lateral to brainstem, along surface of pons and cerebellum	V, VI, VII, VIII	SCA AICA	Superior Petrosal Vein
Premedullary	Anterior to medulla, between the medulla and clivus	XII	Anterior Spinal Arteries	
Prepontine	Anterior to pons, rostral to premedullary cistern		Basilar Artery	

CN - cranial nerve, PICA - posterior inferior cerebellar artery, SCA - superior cerebellar artery, AICA - anterior inferior cerebellar artery.

ifests as a loss of high frequency tones and a reduced ability to discriminate speech.[1, 14, 17, 18] Patients often complain of difficulty carrying on telephone conversations and on average, report reduced hearing for a period of 4 years prior to their diagnosis of acoustic neuroma.[1, 14, 18] Acute hearing loss occurs in a minority of individuals (~ 10%), primarily in younger patients with large tumours.[1, 14, 17, 18] The precise mechanism that underlies hearing loss is uncertain, but may be related to direct compression of CN VIII, reduction in the blood supply to CN VIII or to the cochlea itself. However, because neither the severity of hearing loss nor the reduced ability to discriminate speech correlate with tumour size, the etiology of these neurological deficits is likely multifactorial.[17] Tinnitus is experienced by approximately 70% of patients with acoustic neuromas and is thought to be caused by neural or vascular compression.[1, 14, 17, 18] The tinnitus is often persistent and high-pitched, occuring ipsilateral to the tumour.[14] Dysequilibrium is the third most common symptom produced by acoustic tumours, with an incidence that correlates positively with tumour size.[1, 14, 17, 18] However, if tumour growth is slow, the ipsilateral vestibular deficit may be sufficiently gradual to allow compensation by contralateral vestibular input preventing true vertigo.[14]

Acoustic tumours that extend into the cerebellopontine angle frequently cause anterior displacement of the facial nerve (CN VII), compressing it against the anterior surface of the tumour capsule (Figure 1).[8, 14] Signs and symptoms caused by compression of CN VII include facial weakness and alterations in taste sensation.[1] Further extension of the tumour rostrally can displace the trigeminal nerve (CN V), compressing it between the tumour mass and the tentorium cerebelli. Signs and symptoms produced by compression of CN V include facial hypesthesia/anesthesia (often in the distribution of the second division of CN V), otalgia, and ipsilateral reduction or loss of the corneal reflex.[8, 14, 17, 18] Rarely, compression of CN V or VII results in symptoms that mimic microvascular compression syndromes such as tic douloureux or tic convulsif, complicating the clinical presentation of acoustic neuromas.[14, 15, 18] Caudal extension of the acoustic tumour occurs less frequently, but may displace the glossopharyngeal (CN IX), vagus (CN X) and accessory nerves (CN XI), producing dysarthria, dysphagia, and hoarseness.[8, 14, 17]

Extensive tumour enlargement leads to compression of the brainstem and cerebellum.[14] Cerebellar compression contributes to the dysequilibrium experienced by patients with an acoustic neuroma and may also result in an ataxic gait and limb incoordination.[14] Brainstem compression may cause respiratory depression and long tract signs such as hemiparesis.[8, 14] Compression of the fourth ventricle with obstruction of cerebrospinal fluid drainage can cause non-communicating hydrocephalus and elevated intracranial pressure that may manifest as headache, nausea, vomiting, reduced visual acuity, diplopia, or obtundation.[8, 14, 16, 17] Without intervention, tonsillar herniation secondary to posterior fossa mass effect may ensue.[14]

Diagnosis

Diagnosis of acoustic neuroma requires a thorough history, otological, and neurological examinations. Otologic findings are

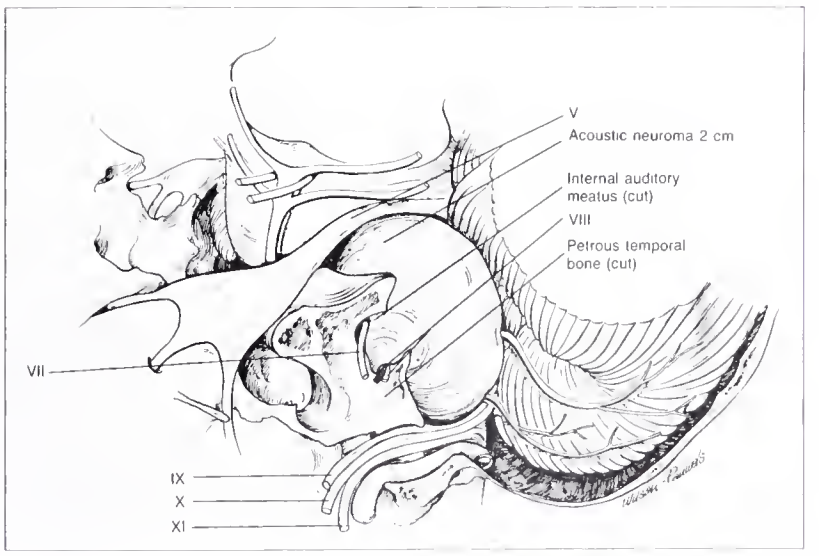

Figure 1. *Schematic of a large acoustic neuroma within the left cerebellopontine angle, depicting displacement of adjacent cranial nerves, the cerebellum and brainstem.*

consistent with a sensorineural hearing loss and may include a unilateral reduction in hearing, an ipsilateral positive Rinne test and a Weber test lateralizing opposite to the ear with the hearing deficit. On neurological examination, the cranial nerve signs and symptoms described previously may indicate the presence of a cerebellopontine angle lesion. Audiometric testing (i.e. pure tone audiograms, speech discrimination) can provide a baseline measurement to aid in the choice of treatment and in evaluating post treatment hearing function. In patients with an acoustic neuroma, pure tone audiograms often show a sensorineural loss of high tones.[8, 14, 17] Poor speech discrimination suggests that the lesion is retrocochlear, with severity often related to the extent of auditory nerve fiber loss.[14] At present, the most reliable, non-radiologic test for acoustic neuroma is the evaluation of brainstem auditory evoked potentials, which measure the changes in electroencephalographic responses to auditory stimuli.[14] Additionally, caloric testing evaluates vestibular function by stimulating the vestibular apparatus with water and measuring the duration of the resulting nystagmus. Specifically, this tests the function of the horizontal semicircular canal, which is innervated by the superior division of the vestibular nerve.[14]

When acoustic neuroma is highly suspected, initial radiologic evaluation may be more cost-effective than audiometric or electrophysiologic testing.[20, 21] Thin-slice axial plane magnetic resonance imaging (MRI) with gadolinium enhancement shows acoustic tumours as round/oval enhancements centred on the internal auditory canal. This procedure has a sensitivity of 98%, a low false positive rate, and can reveal lesions with a diameter of only a few millimeters (Figure 2).[6, 8] Computed tomography (CT) may also show widening of the internal auditory canal due to bony erosion by the tumour.

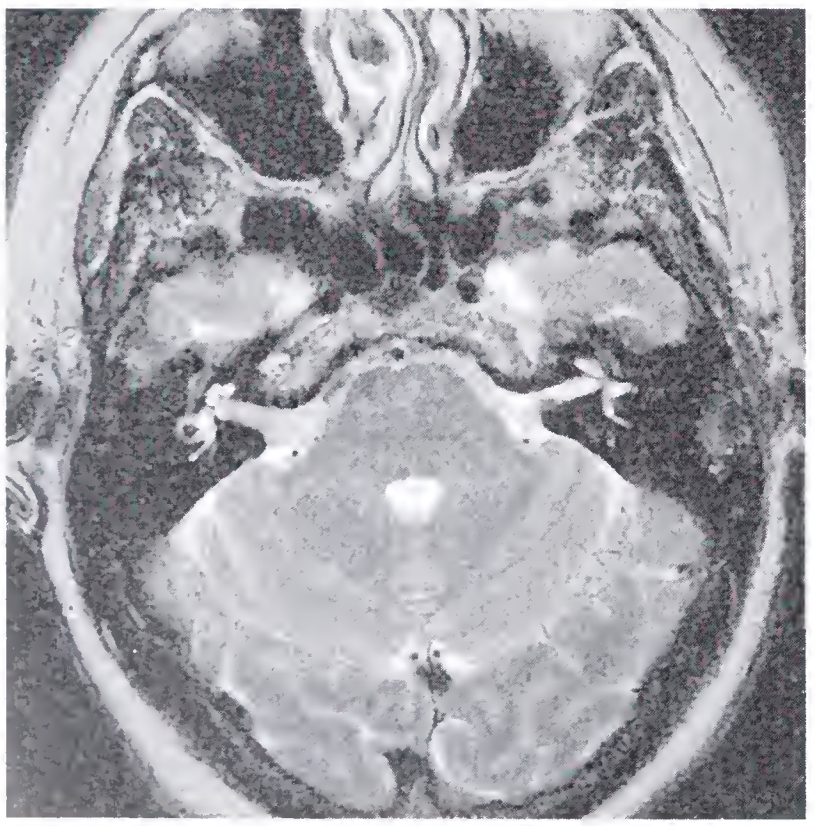

Figure 2. *An axial T2 - weighted MRI without contrast, revealing a right-sided acoustic neuroma extending from within the internal auditory canal into the cerebellopontine angle*

Treatment

The choice of management strategy is dependent upon several factors, including the patient's general health, symptomatology, tumour size and growth rate, hearing function, past attempts at treatment, and the presence of bilateral tumours.[6, 8, 18, 22, 23, 24] Three strategies are used to treat acoustic neuromas: expectant management, radiotherapy and microsurgery. Expectant management involves monitoring the patient for clinical or radiological signs of tumour progression. Serial audiometry and imaging (CT or MRI) is performed annually until tumour growth plateaus. This is a reasonable alternative for patients with asymptomatic tumours, with a tumour in the only-hearing ear, with high operative risks, or who refuse surgical intervention.[25, 26] Microsurgical or radiotherapeutic intervention is advised if the rate of growth exceeds 2 mm per year. [8]

Radiotherapy can be effective at halting tumour growth and reducing the size of small or medium-sized intracanalicular tumours.[27] Up to 98% of patients undergoing radiotherapy may not require further surgery.[29] Two forms of radiotherapy are used to manage acoustic neuromas: Gamma Knife and Linear Accelerator (LINAC). Gamma Knife radiotherapy involves stereotactically-guided irradiation of the tumour using multiple [^{60}Co] sources that surround the patient's head.[29] This treatment allows for tumour control rates of up to 95%.[27] LINAC also delivers photons derived from a single [^{60}Co] source, thus providing a high dose at the tumour site with minimal peripheral radiation by rotating the source about the patient's head.[29] However, irradiation of irregularly-shaped targets is more difficult with LINAC, and there is a higher risk of injury to surrounding structures. Recently, the approach of fractionation, delivering the total dose of radiation over several days, has been applied to LINAC methods and has been shown to reduce the incidence of post-treatment cranial neuropathies when compared to single-dose LINAC.[29] While radiotherapy may preclude the need for surgical intervention, it increases the risk of trigeminal neuropathy, hydrocephalus, and exposure of normal brain tissue to radiation with unknown risks of inducing secondary tumour formation.

Microsurgical resection is considered the standard treatment modality for acoustic neuromas.[6, 8, 17] Three surgical approaches, translabyrinthine, suboccipital, and middle fossa, are commonly used. The translabyrinthine method involves drilling through the mastoid portion of the temporal bone and the vestibule between the external auditory canal and the sigmoid sinus.[8, 17] This method allows for early identification and protection of CN VII, avoidance of cerebellar retraction, a lower risk of injury to caudal cranial nerves, visualization of the anterior brainstem, and good access to the tumour bed to control any postoperative complications that may arise.[6, 8, 17, 23] However, this approach also results in obligatory iatrogenic hearing loss in the affected ear, potentially longer operating time, and difficulty visualizing the brainstem with large tumours.[6, 8, 17]

The suboccipital method involves performing a craniotomy in

the angle of the transverse and sigmoid dural sinuses, and approaching the tumour via the angle between the cerebellum (medially) and the petrous temporal bone (laterally). This approach permits good tumour exposure (regardless of size), excellent control of bleeding (especially around the brainstem), and the possibility of preserving both CN VII and CN VIII (cochlear portion) function.[6, 8, 17, 30] Disadvantages include late identification of CN VII, the risk of cerebellar injury due to retraction pressure, and increased difficulty in removing tumour from the internal auditory canal without violation of the vestibule during drilling.[8, 17] Use of an endoscope during this procedure may overcome some of these disadvantages by allowing better visualization of residual tumour at the lateral end of the internal auditory canal as well as exposed petrous air cells not seen with the operating microscope.[31, 32]

Of these surgical approaches of acustic neuroma resection, the least commonly used is via the middle fossa. This involves accessing the tumour from above after retracting the temporal lobe rostrally, and drilling through the roof of the internal auditory canal. Advantages of this approach include good exposure of small intracanalicular tumours and the possibility of hearing preservation.[6, 8, 17] However, there is limited exposure available via this method, and there may be an increased risk of facial nerve palsy and injury to the temporal lobe secondary to retraction.[8, 17]

The frequency of usage of the suboccipital approach versus the translabyrinthine approach are now approximately equal (50% versus 45% respectively), while the middle fossa approach is used in only 3% of cases.[17] Several criteria have been developed as aids in deciding the best surgical approach for patients with tumours of varying severity.[18, 22, 23] Discrepancies between these criteria stem from differences in their definitions of serviceable hearing, tumour size classification, and surgeon preference for a particular approach. One system currently in use groups patients into the following categories: elderly patients (over age 70), patients with small tumours (2.5 cm or less) and serviceable hearing, patients with small tumours and poor hearing, and patients with large tumours (3 cm or more) regardless of their hearing status.[22] The suboccipital approach is used to resect small tumours in patients with serviceable hearing. The translabyrinthine approach is used to treat all large tumours and small tumours in patients with poor hearing.[22] In the elderly, small asymptomatic tumours are managed expectantly with yearly CT scans and clinical exams.[22] If their tumours are causing symptomatic hydrocephalus, surgery is performed to insert a cerebrospinal fluid shunting device.[22] Large tumours with progressive symptoms in the elderly are treated surgically according to the same criteria indicated above.[22]

The surgical treatment of acoustic neuromas is still fraught with complications. A common complication is the development of cerebrospinal fluid (CSF) fistulae, which occurs in up to 35% of cases and manifests as CSF rhinorrhea, otorrhea, or surgical site drainage.[8, 18, 31, 33, 34] The majority of these fistulae resolve with subarachnoid lumbar drainage, although some require surgical closure.[18] Complications related to cranial nerve injury are common. Of these, palsies of CN VII are often the most distressing for patients.[6] Despite the fact that the majority of patients with acoustic neuromas have normal facial nerve function preoperatively, up to 44% have impaired facial function postoperatively.[17] In addition to possible disfiguring facial weakness, facial palsies increase the risk of exposure keratitis and corneal ulceration, and care must be taken to protect the eye from these sequelae. Injuries to CN VIII are also common.[33] The vestibular portion of the nerve is rarely spared in surgery and postoperative vertigo, dizziness, and nausea and vomiting are common. In addition, the cochlear portion is frequently injured, with up to 75% of patients exhibiting a decline in hearing function postoperatively.[17]

Summary

Acoustic neuromas are common tumours of the posterior cranial fossa. Despite being histologically benign, these tumours cause significant morbidity as a result of localized growth, with resultant compression and displacement of adjacent neural structures. Without medical intervention, severe neurological compromise due to brainstem compression and cerebellar herniation may result. Improvements in diagnostic ability and innovations in both surgical and non-surgical forms of management have lead to earlier and more effective treatment of these tumours with an emphasis on reducing the associated morbidity to the patient. However, significant morbidity is still associated with the management of this disease. Therefore, patients must be informed of all treatment options and given realistic appraisals of expected functional outcomes for each modality in order to decide on the most appropriate course of management.

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Antiglucocorticoid Treatment in Depression

Michael Lewis, B Sc (OT1)

Abstract

Hypercortisolism and resistance to dexamethasone suppression are common findings in major depression. The degree of hypercortisolism has been shown to be related to the severity of depressive symptoms. Adrenal cortisol secretion is known to increase in response to a wide variety of stresses, including psychological stress. Several investigators have theorized that the hypercortisolism associated with depression is a prototypical secondary stress response. Recently, investigators have begun to examine the effect of pharmacologic reduction of cortisol levels in depressed subjects. A series of small open trials and controlled trials suggest that antiglucocorticoids have antidepressant activity in hypercortisolemic depressed patients. Furthermore, findings from these trials suggest that adrenal hyperfunction associated with depression may not be a secondary epiphenomenon. This paper examines the role of hypercortisolism in major depression, the importance of accurate titration of antiglucocorticoid agents, and discusses the potential of antiglucocorticoid therapy for patients with major depression.

Background

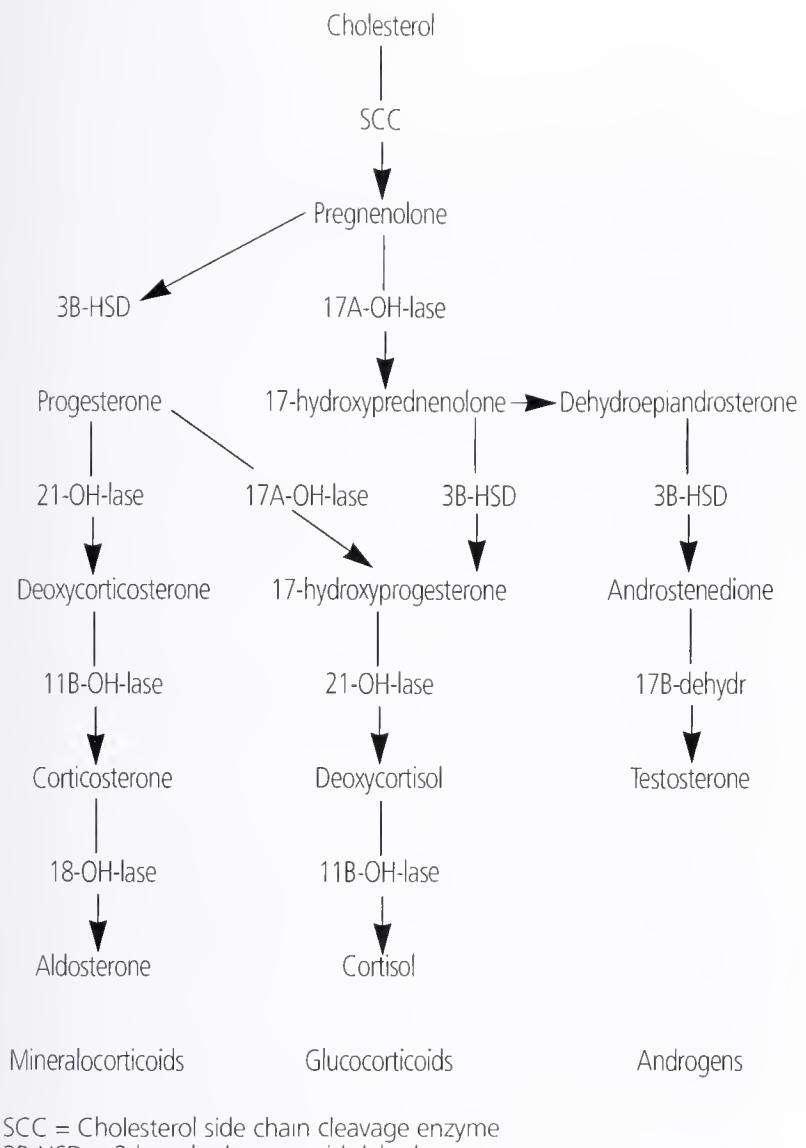
Since the late 1960s, two well-established biochemical abnormalities in the majority of cases of major depression have been observed: hypercortisolism and resistance to dexamethasone suppression.[1] The degree of hypercortisolism in major depression has been shown to be related to more severe symptoms, such as sleep disturbance, pyschomotor disturbance, weight loss, decreased energy, anxiety, delusions, decreased memory, and cognitive impairment.[2,3,4,5,6] Several investigators have theorized that the hypercortisolism observed in depressed patients is secondary to the "stress" of depression.[7]

Adrenal cortisol secretion is known to increase in response to a wide variety of stresses such as surgery, trauma, and infection. Individuals with severe primary or secondary adrenocortical insufficiency must increase their exogenous intake of cortisol in response to such stress. Failure to do so may result in the development of an adrenal crisis. Similarly, it can be argued that patients with severe hypocortisolemia should increase their exogenous cortisol intake in response to significant psychological stress. Jefferies has noted that failure to do so may result in fatigue, malaise, aches similar to that experienced during influenza infection, nausea, vomiting, high fever, low blood pressure, and shock – the signs and symptoms which characterize an adrenal crisis.[8] This suggests that the hypercortisolism associated with the stress of depression may be a necessary biological adaptation.

However, it is also possible that the hypercortisolism associated with depression perpetuates or exacerbates depression. Cortisol secretion may be excessively elevated beyond levels necessary to protect the individual from the stress of depression. Indeed, in Cushing's syndrome, depression is common and usually remits after the hypercortisolemia is treated.[9] Similarly, the pharmacologic administration of glucocorticoids to medically ill patients is also associated with neuropsychiatric symptoms such as emotional lability, anxiety, depression, and cognitive impairment.[10] In order to determine whether the hypercortisolism of major depression plays a pathophysiologic role in some individuals with major depression, it is necessary to lower cortisol levels in depressed patients and measure the effect of such an intervention.

Three medications have been used for the pharmacological reduction of hypercortisolism in Cushing's syndrome: metyrapone, aminoglutethimide, and ketoconazole. Metyrapone is an 11-beta hydroxylase inhibitor and consequently blocks the conversion of 11-deoxycortisol to cortisol (Figure 1). Aminoglutethimide inhibits cholesterol side-chain cleavage enzyme thus decreasing the production of all adrenal steroids,

including cortisol. Ketoconazole, in doses over 400 mg per day, interferes with several cytochrome P-450 enzymes, including cholesterol side-chain-cleavage enzyme, 11-beta hydroxylase, and 17-alpha hydroxylase, with the net effect of blocking cortisol biosynthesis.[11, 12] Ketoconazole also blocks peripheral glucocorticoid receptors.[11, 12]



SCC = Cholesterol side chain cleavage enzyme
3B-HSD = 3-beta-hydroxysteroid dehydrogenase
11B-OH-lase = 11-beta-hydroxylase
17A-OH-lase = 17-alpha-hydroxylase
17B-dehydr = 17-beta-dehydrogenase
18-OH-lase = 18-hydroxylase
21-OH-lase = 21-hydroxylase

Figure 1. *Steroid synthesis pathway.*

Evidence that Supports Antiglucocorticoid Therapy in the Treatment of Depression

Despite the availability of antiglucocorticoid agents, few studies have reported the effect of pharmacologically lowering cortisol levels in depressed patients. A description of antiglucocorticoid therapy in major depression comes from a review of such therapy by Murphy:[13]

> *"...extreme hypercortisolism and resistance to dexamethasone were observed in a thin, suicidally-depressed young woman with low normal blood pressure and no signs of Cushing's syndrome.[14] She had been admitted on three occasions during the previous year for attempted suicide and had failed to respond to many antidepressants given. Her response to oral aminoglutethimide (Cytadren) and cortisol (hydrocortisone, Cortef) was dramatic. After three days of therapy she exclaimed that 'my head feels clear for the first time in months' (almost the same words used by several other responders). This first patient made such rapid progress that she was able to leave hospital on the sixth day of therapy and to be followed as an outpatient; after eight weeks the medication was discontinued. Cortisol levels and dexamethasone suppression had returned to normal by the end of treatment; she has never relapsed."*

In an open trial, Wolkowitz treated 10 out-patients diagnosed with various subtypes of depression (8 unipolar, 2 bipolar, none of whom exhibited psychotic symptoms) with ketoconazole for 3-6 weeks in an attempt to lower their serum cortisol levels.[15] All patients had at least 1 of 2 pretreatment cortisol values above 12 µg/dl (measured at 4 p.m.) and were medication-free for 2.5 months prior to the study. The ketoconazole dose employed was 400-800 mg on the basis of drug tolerance. Three patients dropped out due to side effects or illness. Of the 7 that remained, serum cortisol levels and depression ratings were decreased.

In another open trial, Ghadirian and colleagues examined the effects of antiglucocorticoid therapy in antidepressant-resistant patients with severe psychotic depression (n=9) or non-psychotic depression (n=11).[16] Patients were treated with aminoglutethimide or ketoconazole with or without metyrapone for 8 weeks. A pre-study medication washout period of 1 week for tricyclic antidepressants and 21 days for selective serotonin reuptake inhibitors was undertaken, during which time patients could use chloral hydrate for insomnia and benzodiazepines for anxiety. A flexible medication schedule was used: patients were started on either aminoglutethimide or ketoconazole. The medication was increased every 4-7 days until the Hamilton Depression Rating Scale (HDRS) score fell below 15. The medication was switched (ketoconazole to aminoglutethimide or *vice versa*) if hepatic enzyme concentrations were elevated 2 times above the upper limit of normal, if side effects interfered with treatment, or if there was an inadequate response to treatment. Metyrapone was added to the regimen if improvement was still unsatisfactory. Of the 17 patients who completed the study, 11 patients responded completely as assessed by a decrease of greater than 50% in the HDRS score to less than 15. Two of the patients responded partially and non-psychotics did better than psychotics.

In another open trial, Thakore and Dinan treated 8 non-obese, otherwise healthy in-patients suffering from depression (5 melancholic, 3 psychotic) with ketoconazole for 4 weeks.[17] Six of the patients were on other medications whereas 2 were drug-free for 6 weeks before the study. Patients were started on 200 mg of ketoconazole and the dose was increased to 400-600 mg over 4 weeks, on a weekly basis, until an adequate response was observed. Five patients recovered from their depression, while the other 3 had decreases in their HDRS scores by less than or equal to 50%.

In a placebo-controlled single blind crossover study, O'Dwyer and colleagues treated 8 in-patients diagnosed with major depression, who were otherwise healthy, with metyrapone and hydrocortisone or placebo for 2 weeks.[18] Six of the patients were medication-free while the others had been on a constant treatment regimen that was not altered during the previous 4

A replacement dose of 30 mg of hydrocortisone was administered as a divided 7.5 mg dose qid. The metyrapone dose was titrated from 500 mg qid to 1 gram qid against plasma cortisol in order to keep cortisol within the physiological range. Six of the 8 patients had significant reductions in their depressive symptoms.

Recently, in a double-blind placebo controlled study, Wolkowitz and colleagues treated 20 medication-free, depressed patients, who were otherwise healthy, with ketoconazole or placebo for 4 weeks.[19] Thirteen of the patients were resistant to prior antidepressant therapy; 7 were never treated before with antidepressants. Ketoconazole was given in doses of 400-800 mg. If the dose was greater than 400 mg, it was given twice daily. The medication was titrated blindly according to subject tolerance. In the depressed patients with hypercortisolism, ketoconazole therapy was associated with improvement in depression ratings. Ketoconazole did not improve depression in non-hypercortisolemic patients. Furthermore, cortisol levels were not decreased in the ketoconazole treated group. The investigators noted that the significance of these finding was tempered by the small number of hypercortisolemic patients who were randomized to ketoconazole treatment (n=3), the relatively short duration of the treatment trial, and the simple method used to assess cortisol status (single reading taken at 4 p.m.). Wolkowitz and colleagues concluded that antiglucocorticoids have antidepressant activity in hypercortisolemic depressed patients and that adrenocortical dysfunction has a causal role in some depressed patients.

The studies described above suffer from their small sample size (n = 8 – 20), relatively short duration (2 to 8 weeks), and the fact that 3 of the 5 studies were open trials. Nonetheless, at this stage, evidence from these trials suggests that antiglucocorticoid treatment may be beneficial to many patients who suffer from depression.

Discussion

Could depression be caused or exacerbated by an inappropriate "functional" hypercortisolism? In her review of antiglucocorticoid therapies in major depression, Murphy argues that, "several lines of evidence lead one to suspect that cortisol itself may not be the important entity in causing depression."[13] Her reasons are the following:

1. Cortisol is not elevated in all depressed patients.
2. Euphoria occurs more often than depression following glucocorticoid administration.
3. In a study by Murphy and colleagues, the Hamilton Depression scores dropped rapidly although 8 a.m. cortisol levels remained high.[20]
4. Giving cortisol at the same time as steroid-synthesis inhibitors did not appear to affect the results.[18, 20]

Although it is possible that other adrenal steroids such as androgens, which are suppressed by antiglucocorticoid therapy, may contribute to depression, the above arguments are not necessarily convincing if some pertinent endocronological concepts are kept in mind.

First, adrenal cortisol secretion fluctuates throughout the day in response to waking (namely, its diurnal rhythm), stress, and several other environmental stimuli such as eating and sunlight. This has undoubtedly resulted in relatively broad "normal" laboratory ranges for cortisol. Some depressed individuals with cortisol levels within the broad "normal" range might therefore be mildly hypercortisolemic. Furthermore, the Diagnostic and Statistical Manual (DSM-IV) diagnosis of depression is a phenomenological diagnosis. It is not prudent to assume that hypercortisolism, *or any specific biochemical abnormality* underlies *all* major depression. If some individuals with major depression do not have hypercortisolism and simply have another underlying abnormality contributing to their depressive symptomatology, this does not imply that in those depressed individuals with hypercortisolism, the hypercortisolism is not of pathophysiologic significance. This is confirmed by the above-mentioned study of Wolkowitz and colleagues.[19]

Second, although glucocorticoids given exogenously in suprareplacement dosages cause euphoria more than depression, in many patcints the euphoria typically proceeds to depression if steroid therapy is continued. Furthermore, with the exception of adrenal insufficiency, hydrocortisone and cortisone acetate (a pharmacologic precursor of hydrocortisone) are seldom used as steroid therapies. It should not be presumed that synthetic cortisone derivatives such as prednisone, prenisolone, or dexamethasone have the same neuroendocrinological effects as the normal hormone cortisol.

Third, although the Hamilton Depression scores dropped rapidly while the 8 a.m. cortisol levels remained high, some of the patients in this study conducted by Murphy and colleagues were placed on ketoconazole.[20] As mentioned above, ketoconazole blocks glucocorticoid receptors and therefore serum levels of cortisol might tend to overestimate post-receptor tissue levels.[11,12] Furthermore, while single morning levels of cortisol were high, it is unclear as to what the level of cortisol secretion was throughout the remainder of the day, which may have been much lower than before treatment. In the same review article Murphy states, "Cortisol levels are of little use because of the feedback mechanism, so that there is a great fluctuation with time of sampling."[13] Serial blood or salivary cortisol levels throughout the day would have been more appropriate.

Finally, when Murphy[20] and O'Dwyer[18] gave exogenous steroids to their patients in conjunction with cortisol biosynthetic inhibitors, the dosages of cortisol were approximately subreplacement (20 mg at bedtime) and replacement (7.5 mg four times daily), respectively. The dosages of steroid were not, however, in a typical replacement schedule that mimics the diurnal endogenous secretion of cortisol (i.e., cortisol highest shortly after waking and lowest in the evening). It is therefore difficult to draw conclusions as to the effect of the above replacement therapies on endogenous cortisolemia. It is possible that while the cortisol biosynthetic inhibitors down-regulated endogenous hypercortisolemia, the exogenous dose of steroid partially or near completely replaced remaining endogenous cortisol resulting in a net reduction in serum cortisol. It is also possible that the exogenous dose of cortisol protected the patients from mild to moderate adrenal insufficiency secondary to over-titration of

antiglucocorticoid medication. A mild to moderate adrenal insufficiency would likely not be detectable on laboratory testing as the physiologic range for cortisol is large.

Future Directions

Double blind randomized controlled trials with large sample sizes are required in order to determine the effectiveness of treating depressed patients with antiglucocorticoids. In addition, measurements of pre- and post-treatment serum cortisol levels at several times throughout the day, as well as 24 hr urinary cortisol clearance are necessary. These measures will hopefully help establish hypercortisolemic criteria that would predict which depressed individuals are likely to benefit from antiglucocorticoid therapy. Given that multiple investigations of cortisolemia are expensive and impractical, it will be necessary to develop surrogate markers of hypercortisolism. As an example, dehydroepiandrosterone (DHEA), an adrenal androgen with a longer half-life than cortisol, would be useful as it is subject to less fluctuation in serum levels. This steroid may therefore serve as an effective marker for increased adrenocortical (and cortisol) output. The investigation of other adrenal steroids in this manner may also help to delineate which patients are likely to benefit from such therapy.

Titration methods in antiglucocorticoid therapy need to be carefully explored. The over-titration with antiglucocorticoid drugs may result in mild to moderate hypocortisolemia which may worsen depression or not improve the depression as much or as quickly possible. This important fact has received little attention in the current literature discussing antiglucocorticoid therapy in depression. Indeed, patients with untreated adrenal insufficiency often have psychiatric symptoms including depression (20-40%) manifested by apathy, poverty of thought, and lack of initiative. As well, psychosis (20-40%) manifested by social withdrawal, irritability, negativism, poor judgement, agitation, hallucinations, paranoid delusions, and bizarre or catatonic posturing is also common in hypocortisolemic patients.[21] These psychiatric symptoms occur early in the disease and may pre-date other physical findings. This suggests that the mild to moderate hypocortisolism of early adrenocortical insufficiency has psychiatric implications. Similarly, mild to moderate hypocortisolemia resulting from over-titration of antiglucocorticoid therapy may also have psychiatric implications.

As serum cortisol levels are generally of little value in monitoring subtle degrees of adrenal insufficiency (or excess), titration using antiglucocorticoid drugs should be based on remission of depressive symptomatology and should proceed very slowly. The subsequent administration of subreplacement dosages of cortisol may have the added benefit of protecting the patient from small degrees of cortisol insufficiency and may, consequently, allow for more rapid dose titration of antiglucocorticoid medication. In the future, surrogate markers of hypercortisolism may also play a role in accurate titration of antiglucocorticoid therapy.

The use of current glucocorticoid inhibitors are not without hazards. Over-titration with antiglucocorticoid medication, without concomitant glucocorticoid replacement, may result in severe adrenal insufficiency with catastrophic results. Antiglucocorticoid side effects are also important. Ketoconazole, in antifungal doses (generally less than 400 mg per day), is associated with a 10% incidence of transient increases in liver enzymes with hepatic injury occurring in less than 1% of patients.[12] Pruritis and gastrointestinal reactions are also common side effects. Side effects from metyrapone include hirsutism, dizziness, edema, hypokalemia, nausea, and rash, though these side effects were reported in patients treated for Cushing's syndrome.[22] If antiglucocorticoid therapy proves to be efficacious, the development of other antiglucocorticoid pharmaceuticals with lower toxicity profiles would be desirable.

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The Basics of Physician Compensation

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Abstract

Compensation indicates professional status, influences quality of life and tempers inter-personal relationships in the work world. Because of this, compensation issues are of great concern to both current and future physicians. Currently, most Canadian physicians are remunerated through a fee-for-service system. However, alternative ways to compensate physicians have been adopted in some provinces. Knowing this, it is recommended that physicians be educated on the new and different compensation programs available across the country. By understanding the programs physicians will be able to make informed decisions with respect to their compensation, and capitalize on these changes. The objective of this article is to describe the traditional methods of physician compensation, review the strengths and weaknesses of these methods, and comment on alternative payment plans. In addition, this paper offers an outline of the components of a compensation package that a physician should review prior to entering into a compensation agreement.

Introduction

Discussion about compensation mechanisms for physicians is a sensitive subject. Compensation indicates professional status, influences quality of life and tempers inter-personal relationships in the work world. Because of this, compensation issues are of great concern to both current and future physicians. Everything, from alternative payment plans to whether young physicians should be expected to work in under-serviced regions, is the subject of public forums and private conversations.

The 1990s have seen hard capping of fee-for-service billings, acrimonious negotiations centered on physician compensation, and budget decreases by provincial governments, leaving doctors wary of other possible changes that affect their compensation. In fact, in 1998, the number one issue cited by physicians as the most important issue facing health care was funding cutbacks.[1] With an average of 22.5% of provincial health care budgets being spent on physician compensation, doctors are increasingly sensitive to the government's influence on their livelihood.[2]

Currently, most Canadian physicians are compensated through a fee-for-service system. However, due to the changing economic environment some provinces have moved toward alternative ways to compensate physicians. For example, as of July 1996, in Ontario there were over 200 alternative payment plans involving over 2000 physicians.[3] In addition to alternative payment plans, new methods are also being adopted to compensate doctors.

Given this fact, it is recommended that physicians be educated on the new and different compensation programs available across the country. Greater understanding will enable physicians to make informed decisions with respect to their compensation and to capitalize on these changes. However, few medical schools adequately prepare students and residents for the harsh reality of the "business" of medicine. Far too often, medical students and residents are not equipped to make informed decisions about compensation, and thus do not take full advantage of the available options when they finish residency.

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The objectives of this article are to describe the traditional methods of physician compensation, to review the strengths and weaknesses of these methods, and to comment on alternative payment plans. In addition, it will outline a compensation package for medical students and residents to review prior to entering into a compensation agreement – components that should be included in a sound compensation plan.

Traditional Physician Payment Methods

Several different physician compensation methods are currently being used across Canada in academic health sciences centres and community hospitals. The decision to choose one method over another is based on several factors including physician desires, the availability of various compensation packages, the strengths and weaknesses of these methods, and provincial legislation. With significant restructuring in the health care system currently underway, it is only by understanding what systems are available that physicians, students, and residents can begin to make decisions about how they wish to be remunerated in the future. In an effort to increase the understanding of why particular forms of reimbursement are used, the basic forms of physician reimbursement are reviewed below.

Salary

Salary is a method of compensation by which the physician is compensated at a constant rate on a regular basis (Table 1). Salaried arrangements can be on a full-time, part-time, or sessional basis.[4] In Canadian academic health sciences centres and community hospitals, salaried positions are becoming more common. Some examples of programs already operating in Canada include:

CHC's (Community Health Centres): These centres provide primary care and social services. Physicians are compensated by salary and programs are globally funded by the provincial government. These have primarily been operated in Saskatchewan and Ontario.

CLSC's (Local community service centres): Located in Quebec, these centres are funded on a per capita basis to serve a defined geographical area. Physicians are salaried.

COOP's (Health cooperatives): Primarily found in Saskatchewan, these programs are managed through a public board of directors with funding being provided after negotiation with the provincial government. Physicians are compensated by capitation or salary.[4]

Table 1
Strengths and Weaknesses of Salary Compensation

Strengths	Weaknesses
No financial incentive for unnecessary services. Expenditures may be contained and health care delivery made more efficient by eliminating unnecessary procedures.[5,6]	Risk of inadequate levels of service. fee-for-service doctors report working 1.6 hours more per week in direct patient care than salaried doctors.[3,5]
Ability for hospital administration to control the costs associated with practice.[5]	No incentive to increase productivity.[5]
A high degree of income security exists allowing physicians to diagnose and treat patients as they deem appropriate without the influence of financial incentives.[3]	Physicians perceive a net loss of income.[5]
Administration is simplistic, saving time and money. Thus, health care dollars can be used for services as opposed to administration.[3]	The plan does not respond to individual performance.[3,5]
Physician wages can be scaled on the basis of physician ranking, training, and area of specialization.[3,5]	No incentive for continuity of care because reimbursement is not linked to patient location and needs.[3]
More time is dedicated to other tasks which contribute to the academic setting. Salaried physicians reported working 5.6 hours more per week in administration, research and teaching activities compared to their fee-for service colleagues.[3]	Physician autonomy is perceived to be reduced.[5,7]
Incentives for involvement in continuing medical education and administration. A physician does not lose income when he goes to a conference or meeting.[5,6]	Reduces the ability of the government to influence the specific service initiatives through fee incentives.[5]
The systems encourage attention to preventative medicine.[3,5]	
It is easier to build a team-based integrated system; education, peer review, reporting of clinical outcomes.[3,5]	
Control in the system allows for the rational planning of physician allocation and movement within a given geographical area, and can thus be used to promote practice in under-serviced areas.[3,5]	
Doctors have a controlled work week with the associated lifestyle advantages.[5]	

Salaried positions have previously been uncommon in Canada since physician autonomy was desirable.[2] Salaried employees have employers and, previously, physicians have not found the provincial ministries of health to be acceptable employers.[2] More recently, some physicians have sought salaried remuneration in an effort to gain and maintain personal security. With the introduction of alternative payment programs, hospital management and other third parties have become the "employers", thus decreasing physician anxiety over the prospect of an employer that is removed from them.

Capitation

Capitation is a method of physician compensation in which the payment a physician receives is a periodic fee for each enrollee over a specified period of time (Table 2).[9] Services provided by physicians in a capitated system may be supplied on a global or on a partial basis. Global services provide patients with a comprehensive health care package, whereas partial services only provide a portion of all the services that may be required by a patient. In this compensation system the physician incurs the cost of each service he/she provides (blood work x-rays, etc.) and pays for it from the periodic fee. The doctor's income is derived from the difference between the fee and the costs incurred for each patient [Periodic Fee – Cost of Service = Doctor's Income]. In Canada, capitated systems have not been widely used. However, some provincial governments have operated programs that provide primary care services in which physicians are compensated by capitation.[4] For example, some physicians working in the health cooperatives in Saskatchewan receive their income through a capitation system.

This form of physician compensation has been infrequently used in Canada since the system does not support delivery of health care in small service areas – a significant factor in our large underpopulated country. In addition, a study published in 1996 by Hutchison *et al.* concluded that there was no statistical

Table 2
Strengths and Weaknesses of Capitation

Strengths	Weaknesses
Performance pay system. Income incentives do exist: 1. Physicians must provide sufficient service or their patients will seek other doctors for care.[3] 2. The more efficient a doctor is at providing services, the greater the economic benefits he will receive.[5,8,9]	The possibility of under servicing patients exists.[3,5] A U.S. congressional report in 1994 noted that cost-based denials of treatment occurred "far too often" due to the temptation to make more money by denying care and that this seriously jeopardized patient/physician relationships.[10]
The choice of treatment methods and timing is not influenced by financial incentives or the profitability of service. Thus, there is less incentive to provide excess service.[3,11]	Expected reductions in hospitalizations per enrollee have occurred in capitated systems. However, increases in length of hospital stay and number of hospital visits have resulted. This suggests physicians are waiting longer to hospitalize patients due to the costs they will incur. Thus, patients are more sick on admission and take longer to recover.[12]
The physician's focus changes from the number of services provided to the level of responsibility accepted.[13]	
Greater attention is focused on preventative medicine; establishing a relationship between a physician and a patient even in the absence of illness.[3]	Patients are limited in their choice of physicians for a specified period. In some capitated programs patients often cannot change doctors because only one physician has received their periodic fee.[3]
Integrated health care organizations enhance continuity of care and assist in reducing duplication by improving the coordination of services. [5,7]	Adverse risk selection may occur due to the high cost of care of those most in need (i.e., the elderly).[5]
An optimally sized patient practice is developed in this system.[5] Physicians can control the number of people they take on to their rosters.	Physicians' fees do not reflect patients' frequent demands at inconvenient times[3] since a doctor cannot charge a service fee for each visit.
Administration burdens are eased: 1. The cumbersome administration of a fee-for-service system is eliminated.[11] 2. Services and procedures do not need to be unbundled for payment purposes.[5]	The system is not conducive to medical education. Staff physicians will lose money due to resident/medical student inefficiencies, both in time used in clinic as well as unnecessarily ordered laboratory tests and radiographs.
Financial stability is improved. Providing a predictable financial outlay for comprehensive care programs allows hospitals to set priorities and allocate resources. As well, payment certainty at the beginning of the month improves physician cash flow.[3]	The system does not support delivery of health care in small service areas. It only works well where there is a large population base to support it.[5]
	Variation in physician case mix among doctors may create the illusion or reality of unequal work for similar pay.[3]
	The maintenance and monitoring of health outcomes, and setting and refining of capitation rates under a new database would be costly and cumbersome.[5]

difference in Canadian hospital use among patients of physicians in a capitation-based practice vs. rates among those in fee-for-service practices.[15] Therefore, a capitated system did not prove to control the costs associated with patient care any better than the fee-for-service system. Thus, the risks of under servicing patients[4, 6, 11] in a capitated system, coupled with evidence that hospital utilization is not reduced,[13] suggests this method is not the most desirable from both an economic or medical point of view.

However, it should be noted, that there are no incentives in the Canadian health care system to encourage physicians to control hospital utilization, even in a capitated practice. This is in stark contrast to the American capitated programs in which hospital usage is curtailed because of the cost to the physician with each additional test ordered.

Fee-For-Service

The third classical form of physician remuneration is the fee-for-service system (Table 3). In this compensation method doctors are given a specified fee for any procedure or service provided. A fee-for-service plan may be completely open-ended, with physicians negotiating individual fees with their patients; or it can be based on a fee schedule where the doctor may or may not charge additional fees above the schedule. In Canada, fee-for-service is the predominant form of compensation. In each province a fee schedule is published by the provincial ministry of health for billing purposes. Revisions to the fees are negotiated on a regular basis between the provincial medical associations/societies and their respective governments. All fee-for-service systems are volume driven, and thus a doctor's income is directly proportional to the number and type of services he/she provides.

Fee-for-service is the status-quo compensation method of the Canadian health care system. Currently, approximately 64% of Canadian physicians are remunerated through fee-for-service.[18] This system has provided the autonomy desired by many physicians. However, for those doctors participating in research and teaching, a significant compensation imbalance results since they are inadequately compensated for these tasks. In addition, most provinces have "hard caps" on the levels to which physicians can bill in the fee-for-service system, thus limiting doctor incomes. Due to these issues, the desire of physicians to be compensated through a fee-for-service system has decreased while those who opt for blended and salary forms of remuneration have increased.[18, 19]

Table 3
Strengths and Weaknesses of Fee-for-Service

Strengths	Weaknesses
A "private business" environment for the individual practitioner provides an incentive to work hard. Rewards are directly linked to the output of services.[3,13]	Incentives exist which encourage physicians to over-service patients. Doctors who provide more service receive more income irrespective of who receives the services and the expected effect of providing that service.[4,13]
This plan allows the greatest degree of clinical autonomy.[3]	This system allows the unbundling of services and billing for numerous small services in order to accumulate more wealth.[3,4]
There is an incentive for completeness of care - increased income.[15]	The total cost of the system is unpredictable, and often exceeds budgeted targets since volume, choice and mix of services are not fixed.[4]
Patients are free to choose their own physician.[3]	Physicians experience complete cessation of revenue if there is any interruption in their practice (disability, continued education, etc.).[3]
The plan is based on total cost recovery (the fee schedule for each service provided exceeds the cost of providing the service).[3]	Administration is costly and complex due to the need to monitor the pricing of a wide number of services.[3]
A degree of financial certainty for physicians exists in a fee-for-service system. Physicians are able to calculate their fixed costs and their income, in contrast to a capitated system, where a physician's maximum income is limited, and his fixed costs may change.[16]	The system is not conducive to medical education. Staff physicians will lose money due to resident/medical student inefficiencies, both in time used in clinic as well as unnecessarily ordered laboratory tests and radiographs.
	Encourages physicians to enter specific high paying specialties where they are able to bill more per service.[3]
	This system discourages a multi-disciplinary approach to care.[3]
	There is no incentive for doctors to locate in areas with greater needs if they are able to meet their income needs in the location of their choice.[13]
	Doctors are unable to act as a cohesive body due to differential pricing for different modes of treatment.[3]

Alternative Payment Programs

With the economic uncertainty surrounding the health care field in the 1990s, many Canadian physicians have begun to examine alternatives to the current fee-for-service system. Several models have been created. Each attempts to overcome the weaknesses of the classical compensation packages. Many of these plans have been developed to meet physician needs for income stability.[20] In addition, they have been developed to recruit and maintain physicians, particularly those in sub-specialty services at academic health sciences centres.

Most of the new plans are blended programs, combining elements of each of the classical forms of physician compensation. For example, the College of Family Physicians of Canada has developed a blended program which combines a base salary with incentives for patient volume and non-volume related modifiers.[20] Of these alternatives, little evidence exists in the literature as to their financial stability, functionality, and acceptance. However, Haslam has reported that the alternative funding plan at the Hospital for Sick Children in Toronto has resulted in financial stability, encouraged the reordering of priorities, increased research funding, and increased involvement in undergraduate education.[21]

Alternative payment plans are currently in use or are being developed in eight provinces. It is important for new physicians to become aware of the alternate payment plans that exist in the provinces they work in and understand these new compensation methods since they have significant ramifications on their net income, benefits packages, and lifestyles.

Reward Systems

Organizations today focus on developing a vision and implementing specific tasks to achieve their goals. In order to achieve their goals they must attract and retain the people who are capable of accomplishing specific tasks through the use of rewards. A reward system must stimulate desired behaviours from the employee towards specific organizational goals. In the case of a hospital, these tasks include a combination of clinical service, teaching, and research.

The reimbursement a physician receives can be in the form of compensation and non-compensation components. Compensation components include monetary and in-kind services; these programs incorporate both benefits and incentives plans. These components are developed from the compensation philosophy and broader vision articulated by the organization.[22]

A Compensation Package for Physicians

Motivating physicians to achieve the goals of their hospitals and clinics is a challenging task. A reward system and the maintenance of employment equity is key to recruiting and maintaining physician focus on key goals. A good compensation program incorporates both rewards and equity. Thus, when evaluating and choosing a plan, a new physician should be aware of all of the non-compensation and compensation rewards available and the mechanisms by which they can be attained. The following is an outline of the components of a comprehensive package a new physician should consider.

Base Compensation

Physicians must receive base compensation which is representative of their contribution to the hospital or clinic in one of the three forms of classical compensation. Remuneration should be both institution and position-sensitive. This base compensation should be clearly understood by both parties – physician and employer. Regular reviews at agreed upon time intervals should be established between the two parties thus allowing physicians to instigate change in their remuneration if necessary.

It should be noted that individuals may receive base compensation from more than one source – hospital, ministry of health, universities, etc. For example, many physicians employed at aca-

Table 4
Strengths and Weaknesses of Alternative Payment Plans

Strengths	Weaknesses
Incentives built into systems for teaching, research and clinical care.[19,20]	Decreased clinical productivity since most plans are not solely volume based.[19]
Recruitment and maintenance of physicians with sub-specialty training and in remote areas.[7,19]	Additional administration costs since these programs often involve more than one form of classical compensation and have government requirements.[19,20]
Financial stability for physicians.[20]	Alternative payment plans are subject to more government control than fee-for-service system.[20]
Increased research funding.[20]	
Improved lifestyle compared to fee-for-service.[19]	
Increased undergraduate[20] and post-graduate medical education provided.	

demic health sciences centres are affiliated with universities as post-graduate educators while others receive research grants from a variety of sources. Due to this association, these doctors may receive a salary from the university. Physicians should be clear on both the form and sources of their compensation, and that they do not influence each other.

Benefits and Incentives

In the traditional fee-for-service system most physicians must provide for all their own benefits and insurance. However, with the introduction of alternative payment plans, individual benefits packages are supplied to some physicians. Whether or not a physician receives his benefits through his employment, there are several benefits a new practicing physician should attain. If a physician has an opportunity to negotiate his benefits, the following items should be included in the package:

1. Legislated Benefits
2. Canadian Pension Plan
3. Employment Insurance
4. Workers Compensation (in areas where available under provincial legislation)
5. EHT - Health Tax
6. Fringe Benefits
7. Life Insurance
8. Accidental Death Insurance
9. Long-term Disability
10. Extended Health Coverage
11. Dental and Eye Care
12. Semi-private or Private Hospital Care coverage
13. Pension Plan
14. Financial Management Counseling
15. Own-occupation Long-term Disability
16. Canadian Medical Protection Association Dues
17. Academic Enrichment Funding - travel, conference expenses, medical education leave, etc.

Each of these legislated and fringe benefits are essential for physicians to be aware of and negotiate in their practices. They are expensive and have substantial impact on physician net income and, thus, they are well worth combining in a compensation plan.

Income incentives in excess of base compensation are not commonly used to compensate Canadian physicians. However, an incentive system focused on motivating physicians to achieve specific goals can be beneficial to a hospital or clinic. Short term incentives could include premiums for overnight call and weekend work, individual bonuses for exceeding benchmarks for specific programs, spot bonuses for exceptional individual achievement, and gain/sharing plans for individuals that facilitate hospital cost reductions. Long-term incentives could include long-term bonuses for recruitment and productivity, and equity-based savings plans to contribute to physician savings. Physicians should determine if any of these incentives are available to them when they enter into a compensation program so they are aware of their options for negotiation.

Conclusion

Currently, most Canadian physicians are remunerated by a fee-for-service system. However, due to the changing economic environment, alternative ways to compensate physicians have been adopted in some provinces. Knowing this, it is important for physicians to be educated on the new and different compensation programs available across the country. By understanding these programs, and knowing what they require in a compensation package, physicians will be able to make informed decisions with respect to their compensation and capitalize on these changes.

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In the Literature

Yvonne Chan, M.Sc. (0T2) and Stephen C. Juvet, B.Sc. (0T2)

This section of News and Views will present updates of recent advances in the medical and scientific literature. Critical appraisals of selected studies will highlight this section.

Familial "Early to bed, early to rise" Inheritance Pattern Discovered

Sleep preferences in humans encompass a spectrum that ranges from "morning larks" to "night owls." Although animal models predict the existence of human familial circadian rhythm variations, none of the human circadian rhythm disorders are known to be inherited. Advanced sleep-phase syndrome is a disorder that is characterized by disabling early evening sleepiness and early morning awakening. To date, only two cases have been reported in young adults. In the September issue of *Nature Medicine*, the first recorded example of familial advanced sleep-phase syndrome (FASPS) is reported. The first FASPS patient suffered from early sleep onset and waking and recognized a similar trait in some family members; 29 other subjects in three related families are now known to share her condition. The criteria for FASPS include falling asleep before 8:30 pm, awakening before 5:30 am, a single episode of sleep within a 24-hour period, and the development of this particular sleep pattern before 40 years of age. Six FASPS subjects and six unrelated and age-matched normal controls were assessed in hospital over two consecutive nights. For both groups, the length of sleep was in the normal range. No evidence of narcolepsy or other pathologic sleepiness disorders was found in the FASPS subjects. The circadian phase was determined using plasma melatonin and body core temperature measurements. Both were phase-advanced by 3-4 hours in subjects with FASPS. These results suggest a hereditary circadian rhythm variant in humans associated with a short endogenous period. Work is currently underway to characterize the gene(s) implicated in FASPS.

Jones C.R., Campbell S.S., Zone S.E. et al. Nature Medicine. (1999). 5: 1062-1065)

Remote Spatial Memory and Hippocampal Damage

The hippocampus is believed to be responsible for the acquisition and storage of spatial maps and is therefore essential for learning and remembering places. A profoundly amnesic 76-year-old patient (E.P.) with extensive bilateral damage to all components of the memory system of the medial temporal lobe, including the hippocampus, was the test subject. He was asked to recall the spatial layout of the region in which he grew up and subsequently from which he moved away more than 50 years ago. Five other age-matched controls who resided in the same region for a period of time similar to E.P. and subsequently moved away were also identified and tested. E.P.'s performance in the spatial recall and navigation tests was similar or better than that of the control subjects. In stark contrast, E.P. could not navigate in the region to which he moved to after he became amnesic. These results demonstrate that the medial temporal lobe is not the storage site of spatial maps. They also support the belief that the structures in the medial temporal lobe, including the hippocampus, are essential for the formation of long-term declarative memories, but not for the retrieval of remote memories.

Teng E. and Squire L.R. Nature. (1999). 400: 675-677)

Effects of Cigar Smoking on Cardiovascular Disease (CVD), Chronic Obstructive Pulmonary Disease (COPD), and Cancer in Men

Cigar sales in the United States have been increasing dramatically since 1993. In contrast to the extensive information on cigarette smoking, few data are available on the relation between cigar smoking and diseases. In a large cohort study, 17,774 men aged 30 to 85 years enrolled in the Kaiser

Permanente health plan were recruited. To be included, these individuals must never have smoked cigarettes and must not have smoked a pipe at the time of the study. Subjects who smoked cigars (1546) and subjects who did not (16,228), were followed from 1971 to the end of 1995 for a first hospitalization for or a death from a major CVD or COPD, and through to the end of 1996 for a diagnosis of cancer. Results from the multivariate analyses showed that cigar smokers were at higher risk for coronary heart disease, COPD, and cancers of the upper aerodigestive tract and lung compared to non-cigar smokers. These outcomes demonstrated dose-response correlations in that the increased risks were mainly seen in men who smoked five or more cigars a day. Furthermore, a synergistic relation was found between cigar smoking and alcohol consumption in the increase risk of oropharyngeal and upper aerodigestive tract cancers. Thus, the trend of cigar smoking represents a substantial health care concern.
(Iribarren C, Tekawa IS, Sidney S and Friedman GD. NEJM. (1999). 340: 1773-1780)

Cleaved Antithrombin Changes Molecular Conformation and Inhibits Angiogenesis in Cancer

Angiogenesis is the formation of new blood vessels from pre-existing ones. Many solid tumours depend on an extensive newly formed vascular network for nutrition and expansion. Tumour cells induce the formation of a vascular network by secreting angiogenic factors such as fibroblast growth factors and vascular endothelial cell growth factor. Previous studies have demonstrated that many malignant tumours also generate inhibitors of angiogenesis including angiostatin and endostatin. It is becoming evident that the angiogenic phenotype is the result of a net balance between these positive and negative regulators. In a recent article, investigators reported that cleaved serpin antithrombin functions as a potent antiangiogenic and antitumour factor. This conformation is referred to as antiangiogenic antithrombin (aaAT). An *in vivo* mouse model of tumour growth inhibition by tumour mass was used to identify the antiangiogenic activity. Results demonstrated that a small-cell lung cancer cell line NCI-H69, when grown on a mouse flank, inhibited the growth of a secondary implant on the opposite flank by 80%. Selective passage of NCI-H69 cells through culture enhanced this inhibitory ability. An inhibitor of endothelial cell proliferation was detected in the culture supernatants using a 72h proliferation assay. This inhibitor was purified, N-terminally microsequenced and identified as cleaved bovine antithrombin, an aaAT. Further experiments were conducted to investigate if aaAT possesses antitumour activity in mouse models. Immunocompromised mice were injected with SK-NAS cells to induce tumour formation. After the tumours formed, the mice were injected daily with different conformations of antithrombin and vector. aaAT showed antitumour activity similar to that of human angiostatin and endostatin with the exception that aaAT required substantially lower and less frequent dosage. The clinical applications for aaAT and other angiogenesis inhibitors represent potential treatments for cancer and other angiogenesis-dependent diseases.
(O'Reilly MS, Pirie-Shepherd S, Lane WS and Folkman J. Science. (1999). 285: 1926-1928)

A Better Understanding of Cardiomyocyte Apoptosis in Heart Failure

Cytokines related to interleukin (IL)-6 have been implicated in the pathogenesis of heart failure. One member of the IL-6 family is CT-1, which stimulates cardiac myocyte hypertrophy and acts as a survival factor for these cells *in vitro*. Binding of CT-1 and the other members of the IL-6 family to their receptors initiates a signalling cascade involving the protein gp130. Ventricular myocardial-specific gp130 knockout mice were generated (gp130 knockouts involving all cells are lethal at the embryonic stage). Both gp130 knockouts and controls (knockout vector only) were prepared. A microsurgical technique was used to constrict the transverse aortas of the animals in both groups, simulating systemic hypertension or aortic stenosis. Forty-eight hours afterward, the gp130 knockout mice had significantly poorer cardiac contractility, as assessed by echocardiography, than did control mice that received the vector alone. Moreover, the same gp130 knockout mice did not show ventricular cardiomyocyte phosphorylation of STAT3, a molecule downstream of gp130 in the survival signalling pathway. Furthermore, 90% of the gp130 knockout mice died within 7 days (compared with 30% of controls). Histological examination of the ventricles of the mice revealed dilated cardiomyopathy in the knockout group, but concentric hypertrophy in the control group. As expected, there was a significantly greater incidence of apoptosis in the ventricular cardiomyocytes of the knockout mice compared with the control mice. These data indicate that the CT-1/gp130 pathway is involved in preventing the onset of heart failure, and suggest that novel therapies for heart failure might target this pathway.
(Hirota H, Chen J, Betz UAK et al. Cell. (1999). 97: 189-198)

Important Role for Interleukin-13 in Hodgkin's Lymphoma

It has long been suspected that cytokine signalling plays a role in the development of Hodgkin's lymphoma. The malignant cells of this disorder, Reed-Sternberg cells, are rare within affected tissue and, as a result, have been difficult to study. The investigators hybridized cDNAs from Reed-Sternberg cell lines and from several non-Hodgkin's lymphoma lines to a DNA microarray ("gene chip") representative of 950 genes relevant to inflammation and neoplasia. They found that a number of cytokines (IL-5, IL-13 and granulocyte-macrophage colony-stimulating factor [GM-CSF]) and other genes were upregulated in all cell lines. However, only the Reed-Sternberg cell lines overexpressed IL-13 consistently. This was supported by *in situ* hybridization experiments with lymph node biopsies from patients with newly-diagnosed Hodgkin's disease. The IL-13-

expressing cells were also found to express CD15 and CD30, classical markers of Reed-Sternberg cells. Finally, anti-IL-13 antibodies were found to exert a dose dependent reduction in the proliferation of some of the Reed Sternberg cell lines. Those lines that did not respond in this manner may not have responded because of the very high amounts of IL-13 that they secreted. These findings may suggest a role for anti-IL-13 therapy in Hodgkin's disease.

(Kapp U, Yeh WC, Patterson B et al. J Exp Med. (1999). 189: 1939-1945)

Support for Aggressive Cholesterol-Reducing Therapy in Elderly Patients

Some studies have suggested that hypercholesterolemia does not continue to increase the risk of coronary heart disease (CHD) in advanced age. These studies point to the fact that the relative risk of CHD predicted by hypercholesterolemia decreases steadily through the life span. In a position paper for the U.S. National Cholesterol Education Program (NCEP), however, Grundy *et al.* state that relative risk measurements do not take into account the higher absolute frequency of CHD in elderly populations, and therefore that a measurement of "attributable risk" (the difference in risk for CHD in elderly patients with high cholesterol compared to those with low cholesterol) is more appropriate and that the attributable risk for CHD due to hypercholesterolemia increases with age. The authors review a variety of secondary prevention trials that have demonstrated that cholesterol-lowering therapy lengthens life and reduces CHD risk in patients over 65, and express the opinion that primary prevention data for younger patients can be rationally extrapolated to elderly populations. They recommend that with careful clinical judgement aggressive cholesterol-lowering therapies frequently only employed in younger patients can also be extended to this age group.

(Grundy SM, Cleeman JI, Rifkind BM et al. . Arch Int Med. (1999). 159: 1670-1678)

Normal Human Cells Converted to Tumour Cells *In Vitro*

Since the 1980s, it has been apparent that a finite number of genetic "hits" or mutations are sufficient to convert normal cells to cancer cells. This process involves transformation, in which the cells become unresponsive to normal physiological growth restraints, and immortalization, in which the cells become able to divide an indefinite number of times. In a recent article, investigators demonstrated that it is possible to create human tumour cells by creating four such hits. One of the four hits makes the cell immortal, two deregulate the cell cycle, and the fourth provides a constitutive growth signal. In this study, human fibroblast and epithelial cell lines were retrovirally-transduced with three genes. The first, *hTERT*, encoded the catalytic subunit of the enzyme telomerase, which maintained the length of the repetitive DNA at the ends of the chromosomes. This immortalized the cells because it prevented them from losing genetic information while undergoing repeated cell division. The second gene was the large T antigen from the oncogenic monkey virus SV40. Large T disrupted normal cell cycle control in two ways (i.e. two hits): by inhibiting the p53 and retinoblastoma (Rb) tumour suppressor proteins. This made the cells more susceptible to genomic instability. The final gene was H-ras, an oncogene that encoded an activated form of a normal cellular protein that transduced extracellular growth signals. The fact that the cells were able to grow in soft agar medium (i.e. without solid support), indicated that they had been transformed. In addition, the fact that the altered cells were able to form solid tumours in nude mice indicated that they had become tumourigenic. Hence, cancer cells had been created from normal cells. Further work will be necessary to determine whether any additional cellular pathways are affected by the retroviral treatments, and whether the order of transduction of the genes has an effect on the final phenotype.

(Hahn WC, Counter CM, Lundberg AS et al. Nature. (1999). 400: 464-468)

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Prolific Scientist Profiles

Gairdner Awards 40th Anniversary: A Canadian Tradition

Susan Quesnel, M.Sc. (0T2)

This section will offer a glimpse at the people behind the science of medicine, with a focus on those at the University of Toronto. In this first issue, Prolific Scientist Profiles begins with this year's Gairdner Awards, an event hosted annually in Toronto.

This year marks the 40th Anniversary of the Gairdner Foundation International Awards. The Awards are given annually to leading scientists, whose work promises breakthroughs in medical treatment. The foundation was established in 1959 by James A. Gairdner, a Canadian businessman who wanted to reward and encourage medical scientists who have made contributions in the conquest of disease. Although the Gairdner Foundation is a Canadian institution, it recognizes leading scientists from around the world. It is often referred to as the Canadian version of the Nobel Prize in Medicine, although the Gairdner Foundation selects the recipients earlier. Since their founding, 51 of the 249 recipients have gone on to win a Nobel Prize, which means winning a Gairdner award is the most accurate single predictor of winning the better known Swedish prize.

However, the Gairdner is an award in its own right. To celebrate its 40th Anniversary, the foundation organized a week-long program from Oct 14-22, 1999 entitled "Minds that Matter," in which 50 of the world's leading medical scientists participated in mini-symposia in 14 cities across Canada, ending with a three-day symposium and awards dinner in Toronto. The awards, which come with a cash prize of $30,000 each and a sculpture, Le Coeur, are given for two different categories:

1. The Gairdner Foundation International Awards are given to individuals from diverse fields for outstanding discoveries with contributions to medical science.

2. The Gairdner Foundation Wightman Award is given from time to time to a Canadian individual who has demonstrated outstanding leadership in medicine and medical science.

1999 Gairdner Foundation Award Winners

Recipients of the Gairdner Foundation International Award

Drs. Andrew H. Wyllie and H. Robert Horvitz were jointly recognized for their pioneering contributions to our understanding of programmed cell death.

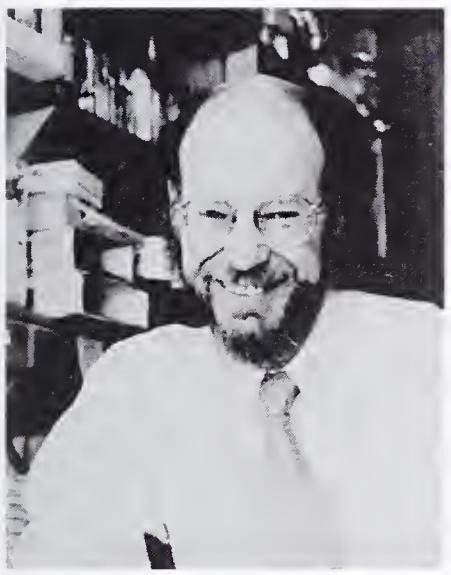
Andrew H. Wyllie, M.B., Ch.B., Ph.D., F.R.C.Path., F.R.S.E., F.R.S.
Cambridge University, Cambridge, United Kingdom

Dr. Wyllie's research has played a pivotal role in bringing attention to the study of programmed cell death, an area that has generated considerable excitement in biology over the past few decades. He was one of the three pathologists in the early 1970's at the University of Aberdeen who noticed the morphological characteristics of a previously described "physiological" form of cell death that accompanies cell turnover. This work was the first to describe the controlled changes in cellular structure that take place during this form of cell death. For this, they coined the term "apoptosis" (Greek for "falling off" of petals from flowers, or leaves from a tree), the pronuncia-

tion of which has become its own subject of debate. The initial studies also provided a link between apoptosis and other processes, such as controlling the growth of neoplasms and tumour regression. Dr. Wyllie's observations formed the basis for the ongoing elucidation of the molecular mechanisms involved in apoptosis, which has provided enormous insight into our understanding of a vast number of processes, such as cancer, development, autoimmune disorders, systemic viral infection, neurodegenerative diseases, tissue toxicity, and ischemic injury.

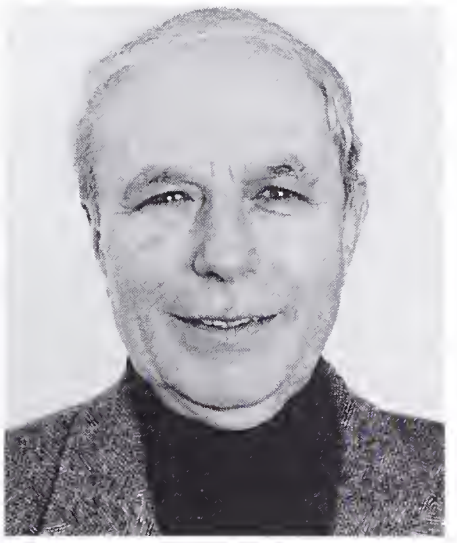
Apoptosis is a field of study that will clearly have an impact on treating human disease, and targeting the regulators of this process is the focus for discovering new types of therapy. Although Dr. Wyllie appreciated the importance of apoptosis during his initial research, even he is surprised by how the popularity of the subject has exploded and reached virtually all areas of medical research today.

H. Robert Horvitz, S.B., Ph.D.
Massachusetts Institute of Technology, Boston, U.S.A.



In his initial research, it would have been hard for a young Robert Horvitz to imagine how his work would eventually complement the findings of Dr. Wyllie. He started off by determining the complete cell lineage of the nematode Caenorhabditis elegans. In the late 1970's, he demonstrated that of the 1090 cells found in the embryo, only 959 are found in the adult (he is often chided that this finding was aided by his degree in Mathematics). Therefore, 131 embryonic cells are programmed to die. The precise nature of this genetic program became the subject pursued by his group and others. His group was responsible for identifying important genes, such as ced-3 and ced-4, whose products are proteases crucial for carrying out cell suicide in this organism in a systematic and orderly way. The human equivalent to these genes and others have been found to be involved in numerous pathways leading to programmed cell death and apoptosis and to play a role in development and many other processes, such as tumour suppression.

Dr. Avram Hershko and Dr. Alexander Varshavsky were both recognized for the discovery of the ubiquitin system of intracellular protein degradation and the crucial functions of this system in cellular regulation.



Avram Hershko,
M.D., Ph.D.
Technion-Israel Institute of Technology, Haifa, Israel

What is known about the ubiquitin system of intracellular protein degradation began with Dr. Hershko's biochemical analysis. He initially observed that protein degradation requires ATP dependent conjugation of protein with a specific polypeptide (ubiquitin). This set the stage in the early 1980's for his group to identify and characterize the multi-component system that degrades proteins and the biochemical steps involved. The 26S complex consists of components of the ubiquitin ligase system, E1, E2, and E3, required for the conjugation of ubiquitin to different types of target protein, and a 20S protease, which forms the catalytic core of the proteolytic pathway. The rapid protein degradation catalyzed by the ubiquitin system is now known to be crucial to progression of the cell cycle, chromosome structure, signal transduction, transcription, development, virology, immunology, and memory. Perturbation of the ubiquitin-dependent degradation pathways is associated with many disease states, including cancer, heart disease and hypertension, cystic fibrosis, muscle wasting, immune invasion by viruses and neurodegenerative diseases.

Alexander J. Varshavsky,
Ph.D.
California Institute of Technology, Pasadena, U.S.A.

Dr. Varshavsky's contribution to the study of the ubiquitin system began as a complement to Dr. Hershko's work. By studying a mouse cell line harboring a temperature sensitive E1 mutant, he was able to confirm the importance of this enzyme in ubiquitin protein conjugation. His research led to further advances in this area by analyzing the nature of the targets of ubiquitination. His "N-end rule" describes the degradation signal that targets a short-lived protein for ubiquitin-dependent proteolysis: a destabilizing amino-terminal residue and a specific internal lysine residue. Dr. Varshavsky has also identified the yeast equivalents of the enzymes involved in this degradation pathway and has highlighted the importance of the ubiquitin system as a component of the stress response system, as well as its importance in mediating progression through the cell cycle.

Recipients of the Gairdner Foundation Wightman Award

In recognition of his outstanding contributions to Canadian [illegible] and medical science as a leader of the Canadian [illegible] medical community:

Charles H. Hollenberg, O.C, M.D., F.R.C.P.(C), F.R.S.C.
University of Toronto, Toronto, Canada

For the past thirty years, Dr Hollenberg has provided leadership to academic medicine in Canada through his influence on education and administration. In his positions as Chair of the Department of Medicine of the University of Toronto and Physician-in-Chief of the Toronto General Hospital, which he held throughout the 1970's, he recruited a large number of clinician-scientists to the department, which blossomed into one of increasing scientific investigation. In his position as the Charles H. Best Professor of Medical Research at the University of Toronto, he played a pivotal role in the creation of the Banting and Best Diabetes Centre for interdisciplinary diabetes research. In 1991, he became President of the Ontario Cancer Treatment and Research Foundation, where he was instrumental in the formation of Cancer Care Ontario, which he served as President and Chief Executive Officer from 1997-1999. The Cancer Care Ontario Practice Guidelines Initiative (CCOPGI) is dedicated to developing the CCOPGI Guidelines, evidence-based clinical practice guidelines (CPGs) on cancer care including treatment, diagnosis, prevention and follow-up. The goal is to ensure that all Ontario residents have timely, equitable access to an integrated system of coordinated and efficient programs in prevention, early detection, care, education and research.

In recognition of his leadership in academic medicine and for outstanding contributions to clinical care and research in respiratory diseases:

Peter T. Macklem, O.C., M.D., F.R.C.P.(C), F.R.S.C.
McGill University, Montreal, Canada

Dr. Macklem has made significant contributions to medicine through both scientific investigation and academic leadership. After obtaining his M.D. from McGill in 1956, he became a Fellow of the Royal College of Medicine in 1963. He has been a leading scientist in respiratory research ever since. He played a crucial part in influencing pulmonary function testing, which he used to explore mechanisms of airway resistance, the site of airway obstruction and its implications for disease. He identified the deleterious effects of smoking on the function of the small airways. He also demonstrated the role of dyspnea and respiratory muscle fatigue in ventilatory failure. In his positions as Director of the Meakins-Christie Laboratories and founding Director of Inspiraplex, the Respiratory Health Network of Centres of Excellence, Dr. Macklem has inspired and influenced many physicians who have also gone on to be leaders in respiratory medicine. As Chair of Medicine at McGill University, he recruited many talented physician-scientists to Montreal.

On how they got started...

Dr. Horvitz

"I was an undergraduate major in mathematics and economics, without any background in biology whatsoever, and as a senior I was advised by a roommate that biology had become interesting. So I registered for a course in my first term senior year in biology and the question was whether it made sense to consider this for graduate school and a possible career. I went to the Professor that taught my introductory biology course and said 'I am majoring in math and also getting a degree in economics and I'm thinking about going into graduate school in biology. Is that ridiculous?' And he replied 'I have my undergraduate degree in economics and my Ph.D. in Physics and I'm teaching your biology course!'"

Dr. Hershko

"I was a medical student and I did one year of research. It was a different project than my present one, but I realized that I liked research. So after I finished my medical studies, I never practiced medicine; I went into Biochemistry. My present project started about thirty years ago, after my post-doctoral training. I became interested in how proteins are degraded in cells because I realized that nobody knew how this was done."

Dr. Varshavsky

"There's a common misconception that people come to science to make discoveries. In fact the best way to see it is to want to enter the subject, to become competent, if not excellent at what you do. Discoveries will come; they will be a function of one's abilities and where you land. The territory of science where you land is determined partly by preference, because you avoid certain things, and partly by accident because some of these things suddenly begin to work and you don't want to leave them. So a lot of these seemingly rational choices at the beginning are anything but."

Dr. Macklem

"...I came to the lab and there were all of these toys. I said to myself, 'I can get paid to play? Why should I ever want to work?'"

Gairdner Foundation International Award Winners from the University of Toronto

1959 - Wilfred G. Bigelow for his contribution to the knowledge of cardiology and especially for his achievement in developing the hypothermia method of open heart surgery.

1964 - Gordon D.W. Murray for his contributions to the knowledge of cardiac physiology and pathology, and the development of several important techniques in cardiac surgery.

1967 - Peter J. Maloney for contributions to immunology and diabetes, including introduction of toxoids for immunization against diptheria and tetanus, the demonstration of antibodies against insulin, and the development of sulphated insulin, which is effective in patients who have become insulin resistant.

1969 - Ernest A. McCulloch and **James E. E. Till** for their development of the spleen colony technique for measuring the capacity of primitive normal and neoplastic cells to differentiate in the body.

1969 - Robert B. Salter for his contribution to an understanding of cartilage degeneration, epiphyseal necrosis, torsional deformation of bone and dysplasia of joints in relation to numerous musculoskeletal disorders, especially congenital dislocation of the hip.

1971 - Charles H. Best for his part in the discovery and development of insulin and for many other contributions to medical research.

1972 - Oleh Hornykiewicz for his elucidation of the biochemical lesion in Parkinson's disease and for other contributions to our knowledge of the physiology of the brain.

1973 - Harold E. Johns for his pioneering work in the development of cobalt and high energy radiotherapy, and for his many other contributions to education and research in the field of clinical physics and biophysics.

1975 - William T. Mustard for his contributions in the area of cardiovascular surgery especially for transposition of the great vessels.

1975 - John D. Keith for contributions to our understanding of the natural history of congenital heart disease.

1980 - Irving B. Fritz for his discovery of the role of carnitine in the regulation of fatty acid metabolism.

1986 - Harald Sonnenberg, along with **Adolfo J. de Bold** and **T. Geoffrey Flynn**, for the discovery and characterization of atrial natriuretic factor.

1989 - Ronald G. Worton, along with **Louis M. Kunkel**, for their contributions to the isolation and cloning of the gene for Duchenne/Becker muscular dystrophy.

1989 - Tak W. Mak, along with **Mark M. Davis**, for contributions to the cloning and sequencing of the gene for the T-cell receptor.

1990 - Lap-Chee Tsui, John R. Riordan, along with **Francis S. Collins,** for contributions to the identification of the gene for cystic fibrosis.

1990 - Victor Ling for his discovery of the role of P-glycoprotein in the development of multidrug resistance of cancer cells.

1991 - David H. MacLennan for his contributions to our understanding of muscle membranes and ion transport.

1994 - Anthony J. Pawson, along with Tony Hunter, for contributions to our understanding of the role of tyrosine kinases in signal transduction pathways that control cell growth.

Reversal of Fortune

Allan K. Grill, B.Sc. (OTO)

This article is a tribute to my medical school peers. As a result of their tremendous effort last year, the University of Toronto Faculty of Medicine has adopted a new grading system. This change was initiated solely by the students, and should serve as a strong reminder of their powerful influence in shaping school policy. Remarkably, the students had to face two difficult challenges to achieve their goal: first, they had to overcome a reputation of apathy; and second, they had to overturn a university-wide decision implemented by the Governing Council.

It was during the 1997-98 academic year that these same medical students were first given a golden opportunity to change the way their grades would be reported. Without reiterating the entire debate that took place at numerous Faculty Council meetings, the Faculty of Medicine arrived at a stalemate regarding a new Honours/Pass/Fail (H/P/F) policy that was designed to replace the existing letter grading system.[1] In the hope of gauging student opinion, the medical students were invited to participate in a referendum; however, only 10% of the student body voted on this issue. Without a strong majority supporting the change, the Faculty Council decided to maintain the grading policy as status quo (i.e. letter grading system).

It remains unclear as to why the medical students chose not to take a more active role. One possible reason for their lack of involvement was that the newly proposed grading system would not have been applied to them. The plan was to have the grading system implemented the following year for the incoming class, while the existing letter grading system would remain for the other medical students (years 2 through 4) until graduation. Unfortunately for the students who were in support of an H/P/F scale, many must have assumed that voting would be futile as the student voice was too weak. Others reported that the referendum should not have been conducted via e-mail because of anonymity concerns. As a student who took an active role in this issue, I believe, sadly, that apathy was the driving force preventing students from voting.

Later that year, by coincidence, the University of Toronto Governing Council appointed a Commission on Grading to investigate the grading policies of the university as a whole. This commission published a report recommending several reasons to change the reporting of students' grades.[2] At that time, methods of evaluation and course grading to assess academic performance varied considerably across the faculties at the University of Toronto; ten distinct grading scales were being used. To eliminate the complexity and confusion, the commission proposed one uniform university-wide transcript. This grading scale was approved quickly by the University of Toronto Governing Council and was to be made effective as of September 1, 1998. Shown in Table 1 is a comparison between the newly proposed grading policy and the existing Faculty of Medicine grading scheme that was to be replaced.

Unlike the first grade-reporting proposal from the Faculty of Medicine, this news caught the medical students' attention and was a source of outrage. This new system would have posed a "negative challenge" to medical students. Under the new policy, a student would have needed to increase his/her performance on exams from 80% to 85% to achieve an "A" grade, while "B" average students would have had to increase scores from 70% to 73%. The fact

that the new grading scale increased the number of achievable grades from four letter grades (A, B, C, F) to thirteen (A+, A, A-...etc.) would have most likely led to an equivalent increase in student competition. A mere 2-3% would now distinguish one student from the next despite a lack of evidence showing that such a narrow margin indicates a significant difference in academic performance. Nevertheless, this would most likely force medical students to spend the majority of their time and energy fervently studying for exams. Under the existing Faculty of Medicine grading system, however, marginal differences were not nearly as highlighted unless a grade fell at one of the three inflection points (i.e. 59%-60%, 69%-70% and 79%-80%). Students were therefore more motivated to explore other interests, such as research or extracurricular activities in order to enrich their medical school experience and develop qualities worthy of a successful residency candidate. The newly proposed grading system would have instead created a student body obsessed solely with marks; surely this was not the educational environment originally envisioned by the Faculty of Medicine.

Table 1
Comparison of Grading Scales

†Existing Grading Scale (Pre 1998)	Newly Proposed Grading Scale (Proposed for Sept. 1998)		
80-100% A	90-100%	A+	(4.0)
	85-89%	A	(4.0)
	80-84%	A-	(3.7)
	77-79%	B+	(3.3)
70-79% B	73-76%	B	(3.0)
	70-72%	B-	(2.7)
	67-69%	C+	(2.3)
60-69% C	63-66%	C	(2.0)
	60-62%	C-	(1.7)
	57-59%	D+	(1.3)
	53-56%	D	(1.0)
	50-52%	D-	(0.7)
0-59% F	0-49%	F	(0.0)

†Four grades available on existing grading scale
(Thirteen grades available on new grading scale)
(Grade point average (GPA) included on new grading scale)

Students who would have been most affected by the grading change were the third year clinical clerks. It is known that the marks one receives in third year carry the most weight with respect to residency programs. In addition, clerks must adjust to the pressure of working in a hospital for the first time and performing competently while under evaluation of a staff physician. Many students have reported that most class averages decrease during clerkship because of increasingly subjective grading practices, and the newly proposed grading system would have highlighted any slight decrease in a student's average. Thus, it seems that clerks would have faced tremendous obstacles to maintain a respectable academic standing.

The Governing Council Commission must have had Bachelor degree programs at the University of Toronto in mind when it made its recommendations for grading changes. The report made no mention of the possible impact these changes would have on other undergraduate programs, such as Medicine. To date, no other Canadian Medical school uses a grade point average in its evaluation process. The Faculty of Medicine was also not given fair opportunity to influence the decision as only three members were invited to the relevant meeting. The clearest oversight by the commission, however, was its lack of student representation. Passing this decision in the summer seemed like a deliberate attempt to avoid any potential resistance from medical students.

Aside from the aforementioned grading system, there was one other option available: an H/P/F scale. In this scheme, one would receive a grade of Honours for any mark 80% or higher, a Pass grade for any mark between 60% and 79%, and a Fail grade for any mark below 60%. The commission offered this scale as a fair alternative for a few programs that were grading students on a Pass/Fail system. It was never intended to be a choice of the remaining programs (i.e. Medicine) already using one of the ten alpha-numeric scales. The students thought, however, that the H/P/F option would be appropriate for the Faculty of Medicine because of its similarity to the old grading system with which they were content. For example, instead of reporting a grade of "A" on a transcript for a mark over 80%, one would receive an "H" grade. The only major difference was that one could no longer distinguish between "B" students and "C" students, as both of these categories would be assigned a grade of "P." The students affected by this change, however, would most likely benefit by being able to spend time on other activities and not have a slight decrease in performance change their grades. By finding this loophole in the commission's report, the medical students had become the proponents of an H/P/F grading system.

Having already discussed this issue at length the previous year, the Faculty of Medicine did not want to reexamine the issue unless it was sure to be endorsed by a strong majority of students. Before reopening discussion at Faculty Council, two strict conditions had to be met by the students in order to prove their support for the aforementioned proposal. These included organizing a referendum across all four years

...ative program, while showing an acceptable participation rate and approval rate of 85% in favour. Regardless of their poor showing at the polls the year before, the medical students persevered. While the first-through third year classes voted in a referendum during their first exam to ensure adequate participation, the fourth-year students (many of whom were doing electives abroad) voted by e-mail. The results were very successful. Not only did 92% of the student body participate in the referendum, but 93% were in favour of an H/P/F grading system. With such an overwhelming majority, it would be inconceivable for either the Faculty of Medicine or Governing Council to oppose the student generated motion. Members of both are well aware that grading is a significant portion of a student's evaluation, and students benefit the most if the marks are able to fairly represent academic performance. Nothing would be gained by a grading system that made students unhappy. As a result, both councils voted unanimously to adopt the motion.

The medical students at the University of Toronto should be proud of the unity, organization, and motivation exhibited during these few months. It is important to have a student body with a strong interest in school policy. Never before in the history of the Faculty of Medicine has there been a student-led referendum with such convincing results. Thankfully, the student apathy that had prevented an earlier grading policy change has now dissipated. Only fond memories of a new H/P/F system, emerging out of a fortunate reversal of a Governing Council decision, remain. As the study of Medicine continues to evolve, students will constantly be faced with similar challenges. Whether the topic involves tuition increases or hospital closures, it is vital for individuals to communicate varied interests. Only then can we be sure that resultant decisions be met with unified compliance.

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Law and Ethics in Medicine

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The Doctor's Duty of Confidentiality: Separating the Rule from the Expectations

Bernard M. Dickens, Ph.D., LL.D.*

Introducing Law and Ethics in Medicine

Welcome to the *UTMJ's* new series, Law and Ethics in Medicine. This section is intended to serve as an introduction to legal and ethical issues in medicine. It will feature articles from experts in the field, as well as from medical students and trainees. One issue will be devoted to answering questions from readers. The goal of this series is to clarify important legal and ethical issues before they become concerns at the bedside. Please direct any comments, questions, or suggestions regarding this column to the Series Editor, Law and Ethics in Medicine at the following e-mail address: editors.utmj@utoronto.ca

About the Author

We start this series with an article that deals with one of the most important legal issues in a physician's professional life: the issue of confidentiality. We are pleased to be able to open this series with an article by Professor Bernard Dickens, one of the world's leading experts in medical law.

Bernard M. Dickens, LL.B., LL.M., Ph.D. (Law-Criminology), LL.D. (Medical Jurisprudence) (London), Fellow, Royal Society of Canada, was called to the English Bar in 1963 and to the Ontario Bar in 1977. He is a Professor in the Faculty of Law, the Faculty of Medicine, and the Joint Centre for Bioethics. Professor Dickens specializes in Law and Medicine, and has taught at the College of Law in London and Columbia University, New York, in addition to the University of Toronto.

Professor Dickens is legal articles editor of the *Journal of Law, Medicine and Ethics*, as well as the co-editor of ethical and legal issues of the *International Journal of Gynecology and Obstetrics*. He also serves as a member of the editorial boards of several journals including the *American Journal of Law and Medicine*. He has been involved in a wide variety of organizations in the field of medical jurisprudence. He was Project Director to the Ontario Law Reform Commission's Project on Human Artificial Reproduction and Related Matters. He has been a consultant on several projects of the World Health Organization including co-authorship of Considerations for Formulating Reproductive Health Laws (Geneva: World Health Organization, 1998), and he is currently working on issues in organ transplantation and tuberculosis control.

His writings include over three hundred publications including books, chapters in books, articles, and reports primarily in the field of medical and health law. In 1990-91, he was President of the American Society of Law, Medicine and Ethics. From 1994, he has been on the Board of Governors of the World Association for Medical Law, becoming a Vice President in 1996. He is a Fellow of the Royal Society of Medicine (London), Chairman of the Human Subjects Research Ethics Review Committee of the University of Toronto, and immediate past Chairperson of the Research Ethics Board of the National Research Council of Canada.

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Abstract

The legal duty to maintain patients' confidentiality is central to lawful and ethical medical practice. Exceptions to the rule of confidentiality are few, but tend to be given such emphasis that medical students may believe they are as significant as the rule itself. Courts excuse breach of confidentiality only when there is immediate danger to life or grave danger to continuing health. Privacy and confidentiality are distinguishable. Those who receive private information, whether volunteered by the patient or under mandatory reporting legislation, are bound by the legal duty of confidentiality.

The Duty of Confidentiality

The duty of the doctor strictly to guard private information about a patient is so fundamental in law and in medical ethics that in principle it requires little repetition. The Hippocratic duty to maintain patients' confidences and the foundational ethical duty of doctors to Do No Harm to their patients combine to prohibit a doctor from engaging in negligent and, even more, deliberate disclosure of a patient's confidential information to anyone outside the circle of those responsible for the patient's therapeutic care. Doctors have faced professional misconduct charges for publicizing information even about other doctors' patients, for discussing their identifiable patients with their own spouses, and for improperly discussing patients' conditions with the patients' family members.

The duty to maintain strict confidentiality is so clear in medical ethics and law that modern cases add little to its emphatic nature. Interest in modern cases arises from the exceptions or limits they present. Unfortunately, this exposes newcomers to medical professional ethics to the risk of distortion. Medical literature may so focus on the few exceptions to the rule of strict confidentiality that medical students fail to grasp the central significance of the rule to professional responsibility. They mistakenly believe that the rule is evenly balanced against exceptions, and that any use they feel entitled to make of patients' confidential information, perhaps in the public interest, is as likely to be covered by an exception as it is to be prohibited by the rule.

In 1992, the Supreme Court of Canada established that doctors and hospitals do not own their patients' information, even when they own the paper, computer system or other material or means that contain it. In *McInerney v. MacDonald*,[1] the Supreme Court demonstrated that though doctors may possess their patients' medical and other information, they do not own it. They serve as trustees who possess information only for their patients' benefit. They must use it properly to advance patients' care and best interests, such as in seeking necessary specialists' opinions, but are not free to disclose it otherwise unless they have patients' adequately informed and freely given prior consent.

Disclosure Among Health Care Professionals

The Supreme Court described the relationship between a doctor and a patient as being fiduciary in nature. That is, doctors are legally obliged to treat patients' medical and other information conscientiously in patients' best interests. They are not free to serve some public or social purpose they favour, however worthy it may be in itself, by releasing information they have acquired about patients. They are similarly not free to serve their own interests, for instance in earning fees from investigators, drug companies or other sponsors of studies, by disclosing identities of patients they know who meet study inclusion criteria. Universities, hospitals and professional licensing authorities consider receipt and payment of finders' fees to constitute serious misconduct, unless patients give informed and free consent in advance to this exploitation of their data.

Patients expect, and the law requires, that relevant information will be made available to all members of a patients' health care team. Patients' consent to this disclosure is an element of their consent to care. Courts recognize the role that the modern medical record serves in a patient's care, and observe how medical and related specialization feeds information into the medical file from a wide array of medical specialists and consultants, nurses, medical technologists, allied health personnel such as social workers, psychologists, perhaps hospital chaplains and health facility administrators. The patient's record provides the means by which health care professionals communicate about the patient with each other, and also with others the patient expects to have access to it in order to advance the patient's health and related interests.

Each of those who have access to the patient's record in order to discharge their legal and ethical duties to the patient is bound by duties of confidentiality. When a patient in a teaching hospital agrees to receive health care services from a medical student, the patient expects the student to be aware of the professional duty of confidentiality, and to observe it strictly as part of supervised training. While students may discuss cases with each other and instructors for advancement of students' knowledge and experience, they must be vigilant to guard identities of patients from whose care the students have acquired their information. In contrast, they may discuss personal details of an identified patient's best clinical care with others who share clinical responsibility for the patient's well-being, since this falls within the scope of the patient's implied consent.

Exceptions to Confidentiality

Because legal exceptions to the duty of confidentiality are very rare, the few instances in which a legal exception has been allowed gain wide publicity, in the medical profession, in the medicolegal literature and sometimes in popular newsmedia. This tends to make an exception well-known and commonplace, risking newcomers to medical confidentiality gaining the distorted impression that the exception is pervasive and widely available. In law, however, the exception rests on the very narrow excuse of necessity to save human life or to prevent serious, imminent harm. Even when allowed, necessity is not

justification for breach of confidentiality. It does not justify a breach in the sense of making it just or right, but recognizes the breach as a wrong that may be excused and not punished. When a court of law finds that the wrong of breach of confidentiality may not warrant punishment, however, a medical professional licensing authority or association may nevertheless impose disciplinary sanctions for the misconduct.

The leading case in which breach of confidentiality was found excusable is the well-known 1976 *Tarasoff* case.[2] This concerned a patient who disclosed to his therapist an intention to kill a girl, and subsequently killed her. In a claim brought on behalf of her estate and family, the therapist and clinic sponsor, the University of California, were found liable for not providing necessary protection. The judgment of the California Supreme Court was that:

> *When a therapist determines, or pursuant to the standards of his profession, should determine, that his patient presents a serious danger of violence to another, he incurs an obligation to use reasonable care to protect the intended victim against such danger. The discharge of this duty may require the therapist to take one or more of various steps, depending upon the nature of the case. Thus it may call for him to warn the intended victim or others likely to apprise the victim of the danger, to notify the police, or to take whatever other steps are reasonably necessary under the circumstances.*

The duty is not limited to psychotherapists, but applies to any practitioner who, according to "the standards of his profession," believes a patient to pose "a serious danger of violence to another." The duty is sometimes expressed as a duty to warn, but giving an identified victim due warning is only one option to discharge the duty "to use reasonable care to protect" foreseeable victims. When future victims are not individually identifiable, such as when a patient threatens violence against a class of persons, notice to the police will usually be appropriate.

The court in the *Tarasoff* case expressed the principle that "The protective privilege [of patients' confidentiality] ends where the public peril begins," showing that patients have no legally protected right to inflict violence or peril on others. It may be observed, furthermore, that protecting prospective victims against suffering violence also serves patients' best interests in protecting them from legal consequences of causing it. The patient in Tarasoff was convicted of second degree murder, and later found not guilty by reason of mental disorder. However, where patients have legally protected rights to follow lawful pursuits that may be obstructed if others gain private medical or other information about them, no breach of confidentiality is permissible even in the best interests of others or of society in general.

Mandatory Reporting Laws

Enacted legislation may compel doctors to give particular information about their patients to others, without patients' consent. Laws on public health, for instance, such as Ontario's Health Protection and Promotion Act, require patients with identified communicable diseases to be reported to the local Medical Officer of Health. Highway traffic legislation requires a doctor to report to traffic licencing authorities the name, address and clinical condition of anyone whose health makes it dangerous for him or her to drive, and child welfare legislation creates a duty for doctors and others to report suspected child abuse to a children's aid society or other provincial child protection authority. Further, the provincial College of Physicians and Surgeons can require access to records for audit and disciplinary purposes.

This legislation limits privacy, but not necessarily confidentiality. "Privacy" and "confidentiality" are often considered synonymous, but they are distinguishable. Privacy involves the right to limit access to one's health information, but confidentiality comes into effect only after that information has been obtained by another person or by an agency. People give up some of their privacy when they receive health care and other services, because the care they require cannot be properly planned or delivered unless those responsible for its provision have the information they need, for instance a person's symptoms, history, characteristics, behaviour and lifestyle. However, those who receive this private information, including those to whom the patient voluntarily surrenders it and those who receive it under mandatory reporting laws, bear legal and ethical duties of confidentiality. Recipients of this private information may use it only for agreed purposes, whether by explicit or implied agreement of the patient or as agreed by the legislature that enacts reporting legislation.

Ordinarily, patients receiving or seeking therapy must be asked whether they agree that their identifiable information can be used for nontherapeutic purposes, such as research. If for any reason they cannot be asked in advance, a research ethics board may have to decide whether a particular research use of identifiable data falls within the scope of a patient's implied consent. Recipients of information under mandatory reporting laws may use it for the purposes for which they receive it, and may release aggregated but not identifiable data, but other recipients may be more limited. For instance in May 1999, a judge in England upheld the Department of Health's statement that it was a breach of patients' confidentiality for doctors and pharmacists to give patients' anonymous, aggregated data to a data collecting company that would sell data on doctors' prescribing habits to drug companies. The breach of confidentiality consisted in using patients' information for a purpose other than that for which it was given.

A Case Study

A March 1999 judgment of the Supreme Court of Canada illustrates the immense caution that must be exercized before a doctor may lawfully break medical confidentiality. Named by pseudonyms, the case indexed as *Smith v. Jones* arose when a lawyer acting for a man accused of aggravated sexual assault of a prostitute referred him to a psychiatrist for a forensic assessment. During assessment, the man described a detailed plan he

had begun to implement to kidnap, assault and murder a prostitute, as a "trial run" for a series of subsequent kidnappings and murders. The psychiatrist diagnosed a paraphiliac disorder manifested by sexual sadism, personality disorder, antisocial disposition and drug abuse, and concluded that the accused man was dangerous and likely to commit future serious offences unless he received sufficient treatment. The man pleaded guilty to the offence with which he was charged, so there was no evidence presented in court of his actions or personality, and the lawyer did not introduce the psychiatrist's report at the sentence hearing.

The psychiatrist was very concerned that, on release after completion of sentence, the accused man would be a danger to the public. However, rather than risk legal and professional liability for taking the information the accused had given him, and the conclusion he had reached, to the police, the psychiatrist wisely initiated his own legal proceedings for a judicial declaration that he was entitled to disclose his information to the police. In a hearing behind closed doors, the British Columbia trial judge granted the declaration, but sealed the Court file against any disclosure, pending an appeal. The provincial Court of Appeal also permitted, but did not require, disclosure to police authorities, but kept the court file sealed until final appeal to the Supreme Court of Canada, where proceedings were conducted in open court, subject to a publication ban.

The Supreme Court recognized that the issue did not concern a therapeutic doctor-patient relationship, since the conduct of the forensic assessment imposed no treatment responsibilities upon the psychiatrist, but it was closely comparable. The Court observed that the integrity of lawyer-client relationships is fundamental to the protection of the public interest in the due administration of justice. Accused persons must be able to speak freely with their lawyers, in the same way that patients must be able to speak to their doctors, secure in the knowledge that what they say will not be divulged without their consent. They must be equally secure that information they are advised to provide to specialists for purposes of their defence will not be disclosed without their approval. The Court found that any exception to the protection of this confidentiality applies to all confidential relationships, such as arise in a therapeutic doctor-patient relationship. Public interest or even protection against unspecified risk will neither justify nor excuse breach of fundamental confidentiality, such as secures clients in dealings with lawyers and patients in dealings with doctors.

The Court ruled, however, that danger of a particularly serious and imminent nature might excuse breach of confidential relationships. The three conditions for this exception are that:

1. There is clear risk to an identifiable person or group of persons;
2. The risk is of serious bodily harm, including serious psychological harm, or of death; and
3. The danger is imminent.

The Court agreed with the lower courts that all of these conditions were satisfied in this exceptional case. Nevertheless, disclosure should be limited as much as possible. Its scope should be restricted to essential information, and only those who need to be informed for purposes of protection should be informed. In this case this meant notifying the police, but in the *Tarasoff* case notification would be allowed only of the girl at risk or her immediate family.

The lessons of the case concern the conditions for breach of confidentiality, and, more particularly, the care the psychiatrist took in ensuring that the disclosure he wanted to make would be lawful. This presents a helpful model of the care with which doctors should treat any incentive they may have to violate medical confidentiality. Confidentiality remains fundamental not only to professional conduct, but also to patients' rights to appropriate medical care. Its compromise is excusable only in the most extreme of circumstances. It is never too early for medical students to learn this lesson.

Disclosure to Patients of Their Own Records

It is no breach of confidentiality that patients are legally entitled to know all of the contents of their own medical records. The Supreme Court of Canada affirmed in 1992 that doctors who possess the information are trustees, and so bound in principle to follow directions of the patients whose information they possess. This is so even when a doctor possesses information obtained or concluded by other doctors, such as those previously responsible for a patient's care.

Patients can accordingly direct that information in their medical records be made available to themselves or to others they identify, such as prospective employers. However, this right of patients does not compel doctors to hand patients their medical files. Doctors must always retain patients' records, in case access to them is required suddenly, such as for patients' emergency care. Copies of raw data in files need not be handed over either, since patients may not understand what is written or, worse, may harmfully misunderstand. Doctors may discharge their duty to afford patients access to the information in their records by answering patients' questions honestly, or by making copies available to others the patients elect who can tell them what the records show, and what the records mean. How patients are given their own information raises legal issues not of confidentiality, but of negligence.

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1. McInerney v. MacDonald, (1992) 2 Supreme Court Reports 138 (Supreme Court of Canada).
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4. Ibid. at 347.
5. R. v. Department of Health ex p. Source Informatics Ltd. (1999) Lloyd's Law Reports, Medical 264 (High Court, Queen's Bench Division).
6. Smith v. Jones (1999), 169 Dominion Law Reports (4th) 385 (Supreme Court of Canada).
7. McInerney v. MacDonald, note 1 above.

Back to Basics

Interpreting the Electrocardiogram

Stephen C. Juvet, B.Sc. (0T2), Yvonne Chan, M.Sc. (0T2), and Robert W. Wald, B.Sc., M.D., F.R.C.P.(C)*

This is the first instalment of a three-part series in which essential diagnostic tests of key importance in medicine will be reviewed.

Introduction

Electrocardiography (ECG) provides a wealth of information about the status of the heart in both physiological and pathological states. Here we describe an approach to interpreting the standard 12-lead ECG in the clinical setting. The majority of common ECG abnormalities are detectable using this method; however, the examples of abnormalities described here are by no means comprehensive.

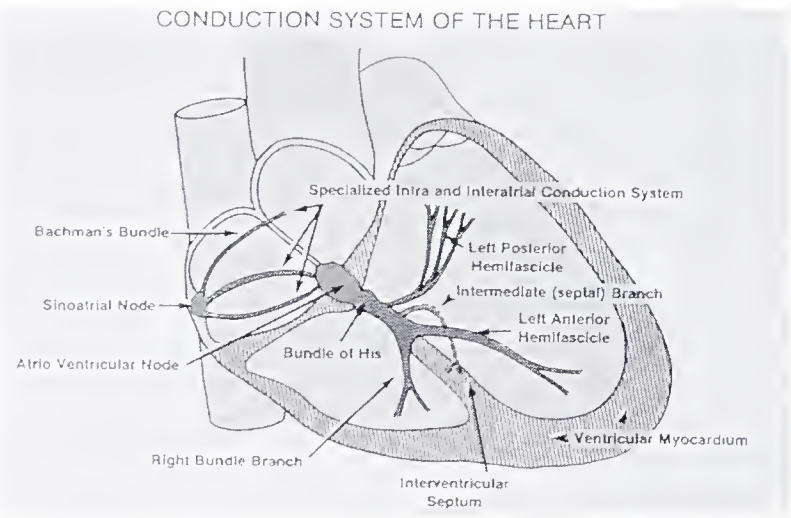

Figure 1. *Major components of the conducting system of the heart.*

This review assumes that the reader has a basic knowledge of both the electrophysiology of the heart and a normal ECG. For reference, Figure 1 depicts the conduction system of the heart in relation to various anatomical structures and Figure 2 depicts a normal adult 12-lead ECG.

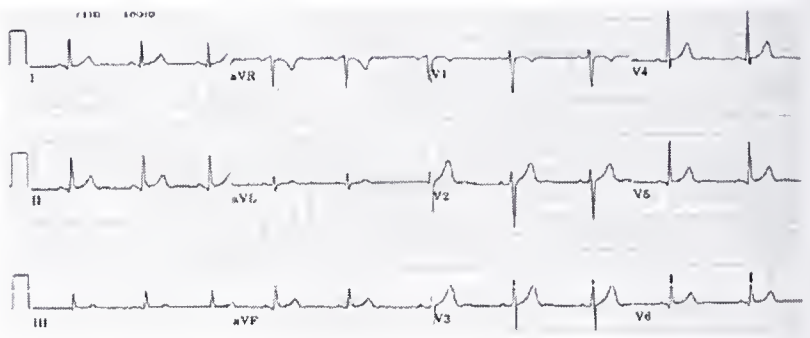

Figure 2. *A normal adult 12-lead electrocardiogram.*

Irrespective of the method used, it is important that a systematic approach to ECG interpretation be taken in order that no abnormalities are missed. It is also worthwhile to emphasize that for any particular patient, electrocardiographic idiosyncrasies are possible. Thus, it is always helpful to compare an ECG tracing to any previous tracings that are available.

Step 1. Determine the Heart Rate

The heart rate is the easiest piece of information to glean from the ECG. Each small square on the trace paper is equivalent to 0.04 s and each large square is 0.2 s; hence 1 s = 5 large squares. The heart rate can be determined quickly by dividing 300 by the number of large squares between two consecutive QRS complexes (this distance is the RR interval). For example, if the RR interval is two squares, then the heart rate is 150 bpm. If the heart rate is irregular or very slow, it is more accurate to count the number of RR intervals in 6 s of a rhythm strip (30 large squares) and multiply this number by 10.

Once the heart rate is determined, it may be classified as:

- **Tachycardia**: heart rate > 100 bpm
- **Normal rate**: 60 bpm < heart rate < 100 bpm
- **Bradycardia**: heart rate < 60 bpm

[illegible] Professor, Department of Medicine and Institute of Medical Science, [illegible] University Health Network, Mount Sinai Hospital, University of Toronto.

Note that in certain circumstances, tachycardia and bradycardia are physiological (i.e. tachycardia following exercise and bradycardia in a seasoned athlete).

Step 2. Decide Whether an Arrhythmia is Present

To identify an arrhythmia, it is most helpful to find the P waves and determine their relationship to the QRS complexes. In **normal sinus rhythm**, a QRS complex follows each P wave and each QRS complex is preceded by a P wave. Disorders of cardiac rhythm are common and produce highly characteristic ECG patterns. Check for PR prolongation, signifying an atrioventricular block, and wide QRS complexes, signifying a ventricular origin of the rhythm.

Cardiac arrhythmias can be classified as **tachyarrhythmias** and **bradyarrhythmias**. The tachyarrhythmias are further classified into premature beats, atrial tachyarrhythmias and ventricular tachyarrhythmias. Note that the terms supraventricular and ventricular refer to localization above or below the bundle of His. Figure 3 illustrates the origins of many arrhythmias in relation to the conduction system of the heart.

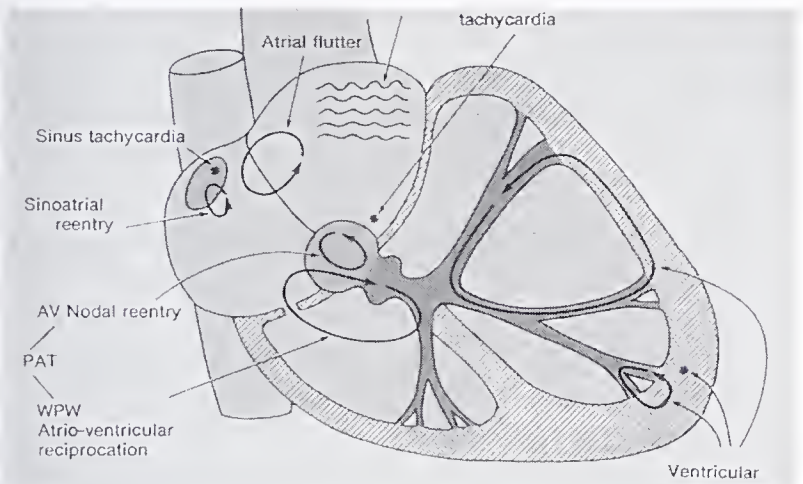

Figure 3. *The major sites at which arrhythmias may develop. Note that many of the major regular arrhythmias (atrial flutter, ventricular tachycardia and paroxysmal atrial tachycardia) arise from the activation of re-entrant circuits.*

2.1. Tachyarrhythmias

Premature Beats

Premature atrial beats (PAB). Occasionally, an ectopic atrial focus (a focus of electrical activity other than the sinus node) discharges. Because this focus is in a different position than the sinus node, the P wave looks abnormal (Figure 4a). The QRS complex that follows a conducted PAB is usually the same as a sinus beat unless there is rate-related aberrant conduction. Junctional premature beats originate in the atrioventricular (AV) node and give rise to retrograde P waves. PABs are usually random events that can occur anywhere in the cardiac cycle and can initiate other atrial arrhythmias, such as atrial fibrillation or paroxysmal supraventricular tachycardia.

Premature ventricular beats (PVB). PVBs are similar to PABs, but originate in the ventricle (Figure 4b). Discharge of a ventricular focus results in wide, bizarre, giant QRS complexes that are common following myocardial infarction (MI), but may be markers of many other cardiac and non-cardiac conditions.

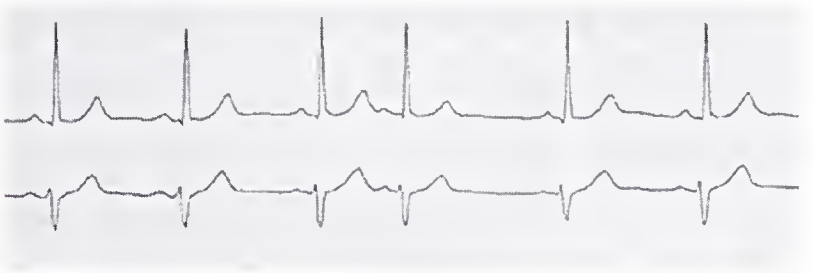

Figure 4a.

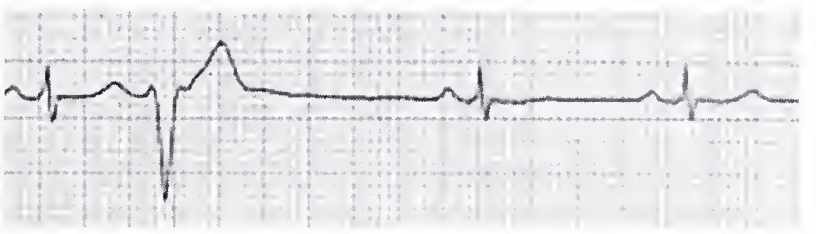

Figure 4b.

Figure 4. *Premature atrial beats (PAB) Figure 4a, and premature ventricular beats (PVB) Figure 4b, compared Note that in both cases, the waves representing depolarization (the P wave and QRS complex, respectively) are altered in the abnormal beats. This indicates that an ectopic focus was the source of the depolarization.*

Atrial Tachyarrhythmias

Sinus arrhythmia. The rate of depolarisation of the sinus node is under the influence of the autonomic nervous system. Respiratory variations in rate are mediated primarily by the vagus nerve and give rise to sinus arrhythmia (Figure 5). Sinus arrhythmia is exaggerated during deep breathing. The heart rate increases with inspiration and decreases with expiration.

Atrial flutter. This is a re-entrant atrial arrhythmia that generates flutter waves (F-waves) at a rate of approximately 300/min. Atrial flutter is responsible for the characteristic "sawtooth" appearance of the baseline of the ECG. The AV node cannot conduct at this rate and a 2:1 heart block develops resulting in a regular narrow QRS complex tachycardia with a rate of 150/min. With changes in vagal tone, higher block ratios may also develop and the rate may be irregular (Figure 6).

Atrial fibrillation (AF). In AF, the ECG baseline is chaotic, resulting from electrical discharges travelling in random circuits (multiple microreentry), which bombard the AV node from ran-

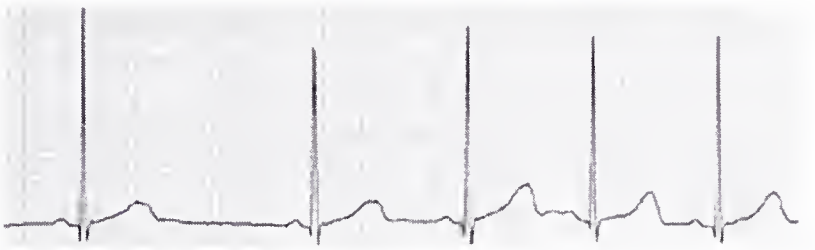

Figure 5. *Sinus arrhythmia. The RR interval varies but the P wave, QRS complex, and T wave are normal.*

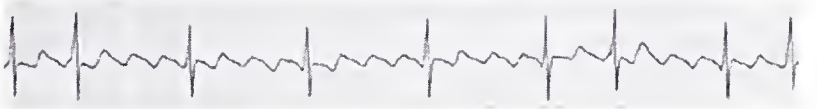

Figure 6. *Atrial flutter. The baseline has a sawtooth pattern and only some of the impulses trigger a QRS complex*

rate directions up to 600/min (Figure 7). There are no P waves and thus no effective atrial contractions. This is important because blood clots may form in the atrium as a result of this arrhythmia. Transmission through the AV node occurs stochastically, resulting in an irregularly irregular frequency of otherwise normal QRS complexes.

Paroxysmal atrial tachycardia, or as it is now known, **paroxysmal supraventricular tachycardia (PSVT),** is a re-entrant arrhythmia either confined to the AV node or one that uses an accessory bypass tract. It is a regular narrow QRS complex tachycardia (rate 150/min or more) characterized by an abrupt onset and termination. PSVTs are generally benign arrhythmias.

Nonparoxysmal or ectopic atrial tachycardia (EAT). EAT arises from an ectopic atrial pacemaker that fires at a rate greater than the sinus node for variable periods of time. The ECG shows a rapid heart rate with abnormal P waves reflecting an ectopic pacemaker (Figure 8).

Figure 7. *Atrial fibrillation. Multiple ectopic foci in the atria fire in chaotic fashion producing an irregular baseline. QRS complexes are triggered randomly leading to an irregularly irregular ventricular rate.*

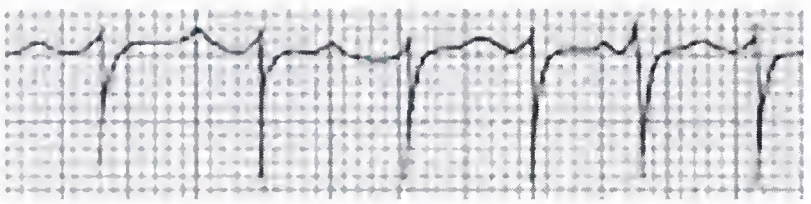

Figure 8. *Paroxysmal atrial tachycardia. An atrial ectopic focus suddenly fires at a faster rate than the sinus node, producing a string of abnormally shaped P waves. Usually each P wave triggers a QRS complex.*

Ventricular Tachyarrhythmias

Ventricular tachycardia (VT). In this potentially dangerous arrhythmia, the ECG contains a series of three or more broad (> 0.12 s) QRS complexes in rapid succession (rate 150-200 bpm; Figure 9). VT may arise from a single ventricular ectopic focus or it may be a re-entrant arrhythmia involving the ventricular myocardium and the distal conduction system. Short runs of ventricular tachycardia are called **non-sustained ventricular tachycardia**. VT is frequently a sign of severe heart disease. It occurs most often after MI, in dilated congestive cardiomyopathy and in severe aortic valve disease. Digitalis toxicity (see below) may also cause ventricular tachycardia. Ventricular tachycardia can deteriorate rapidly into ventricular fibrillation.

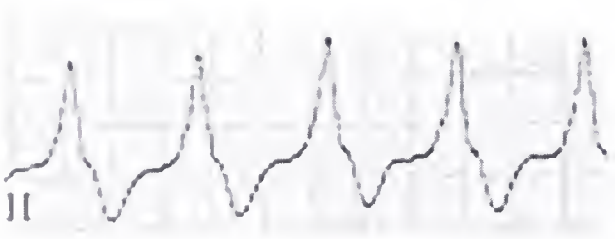

Figure 9. *Ventricular tachycardia. A string of broad QRS complexes dominating, obscuring P waves.*

Ventricular fibrillation (VF). VF is the most severe of all arrhythmias. Ectopic impulses originating in the ventricles lead to re-entrant circus movements of current through random pathways. In all leads, the ECG shows a random baseline (Figure 10). The ventricular myocardium does not contract in a coordinated fashion, effectively reducing the cardiac output to zero. Unconsciousness follows in seconds and death ensues unless defibrillation is successful.

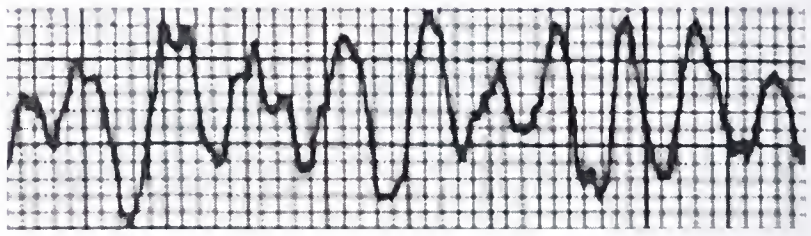

Figure 10. *Ventricular fibrillation. The most severe of all arrhythmias, ventricular fibrillation is characterized by a random, irregular baseline resulting from chaotic ventricular electrical activity.*

2.2. Bradyarrhythmias

The major bradyarrhythmias are due either to abnormalities of impulse formation (sinus node disease) or to an **AV block.** AV block results from abnormalities of impulse conduction through the AV node and/or the ventricular conduction (His-Purkinje) system. It is classified as **first, second,** or **third degree AV block:**

- In **first-degree AV block,** each P wave is followed by a QRS complex, but the PR interval is prolonged to > 0.20s (Figure 11).
- In **second-degree AV block,** the PR interval can become progressively longer until a P wave is blocked. A Mobitz type I second-degree AV block (or Wenckebach block) occurs when 3 P waves occur for each 2 QRS complexes and is reported as a 3:2 block (Figure 12). A Mobitz type II second-degree AV block is an intermittent blockage resulting in a regular block ratio such as 3 P waves to 1 QRS complex, reported as a 3:1 block (Figure 13).
- In **third-degree AV block,** the P waves and QRS complexes show no relationship to one another. Instead, large "ventricular escape" QRS complexes occur at a rate of 40-50 min (Figure 14). Since this may result in shock or syncope, artificial pacing is often used to treat this condition. Bundle branch block, in which one of the bundle branches fails to conduct impulses properly, is described in step 4.

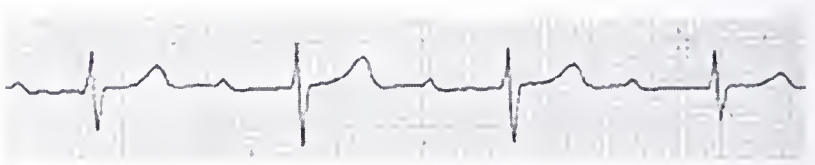

Figure 11. *First-degree AV block. The PR interval is longer than 0.20s.*

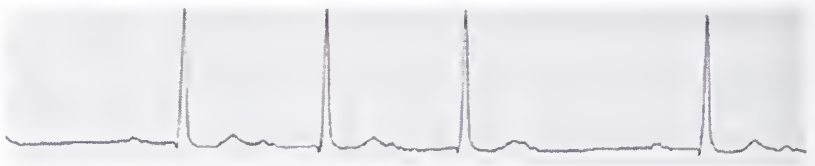

Figure 12. *Second-degree AV block (Wenckebach type or Mobitz type I). The PR interval becomes progressively longer, and a QRS complex is "dropped"*

Figure 13. *Second-degree AV block (Mobitz type II). The PR interval is constant but QRS complexes are lost. In 2:1 block, there is one QRS complex for every two P waves, and in 3:1 block there is one QRS complex for every three P waves.*

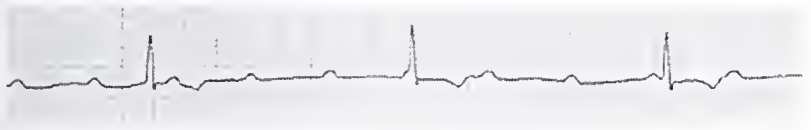

Figure 14. *Third-degree AV block. The ventricles beat at an intrinsic rate of approximately 40 per minute. P waves also occur at a regular rate. However, there is no relationship between the P waves and QRS complexes.*

Step 3. Examine the PR Interval Further

The PR interval represents the time taken for the atrial impulse to be conducted through the AV node and the bundle of His. It is measured from the beginning of the P wave to the beginning of the QRS complex. The normal PR interval is greater than 0.12 s and less than 0.20 s; long PR intervals occur in first-degree AV block.

Short PR Intervals: The Pre-Excitation Syndromes

If the PR interval is consistently short (less than 0.12 s), there is usually an accessory rapid conduction pathway present. This results in pre-excitation of the ventricles which hastens the onset of the QRS complex.

In **Wolff-Parkinson-White (WPW) Syndrome**, the accessory pathway is extra-nodal and inserts into the ventricle at a distance from the AV node. The resultant QRS complex is a fusion beat between the pre-excited and the normal AV node-conducted beat. The upstroke of the QRS, which starts right after or even during the P wave, is slurred. This slurred upstroke is called a **delta wave** (Figure 15) and in addition to shortening the PR interval, it broadens the QRS complex. Arrhythmias arise easily in WPW syndrome for one of two reasons: 1) impulses can be conducted through the normal pathway and then re-enter the atria via the abnormal pathway, which leads to a circus-movement tachycardia (one of the abovementioned PSVTs); or 2) atrial arrhythmias, such as atrial fibrillation, can conduct rapidly through the abnormal pathway, resulting in very rapid and potentially dangerous arrhythmias.

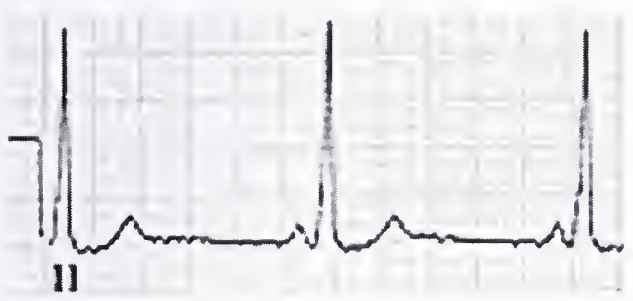

Figure 15. *Wolff-Parkinson-White syndrome. Note the shortening of the PR interval and the widening of the QRS complex by the delta wave.*

In **Lown-Ganong-Levine (LGL) Syndrome** there is an accessory pathway that conducts rapidly but inserts into the bundle of His. This results in a shortened PR interval, but a normal QRS complex without a delta wave.

Step 4. Examine the Width of the QRS Complex

The width of the QRS complex reflects the time taken to depolarize the ventricles. It is measured from the beginning to the end of the QRS complex. The normal QRS complex is 0.08 s (two small squares) or less in width.

QRS Wider Than 0.12 s: Bundle Branch Block

In **bundle branch block,** one of the two main branches of the distal or ventricular conducting system (the His-Purkinje system) conducts slowly or is blocked resulting in a wide QRS complex more than 0.12 s in duration. **Left bundle branch block** (LBBB) is mostly positive, broad and bifid in leads I, aVL and V_6. **Right bundle branch block** (RBBB) is broad, bifid and positive in lead V_1 (Figure 16). LBBB renders the ECG-based diagnosis of MI very difficult and often impossible because Q waves are obscured.

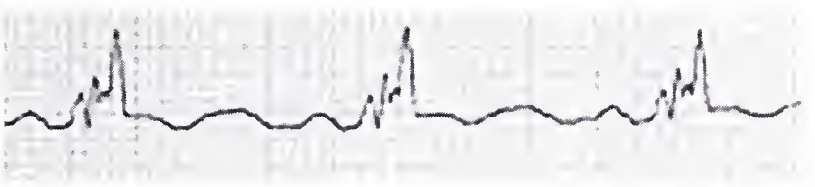

Figure 16a.

Figure 16b.

Figure 16. *Left bundle branch block 16a, LBBB compared with right bundle branch block 16b, RBBB. In LBBB, lead V_5 or V_6 contains a broad QRS complex with a bifid R wave. In RBBB, bifid R waves are seen best in lead V_1 or V_2.*

When the QRS is Only Slightly Widened: Hemiblocks

Slight widening of the QRS (greater than 0.08 s but less than 0.12 s) is a feature of **hemiblock.** The left bundle branch divides into an anterior and a posterior fascicle whereas the right bundle branch is not divided into fascicles. Ischemia or infarction of the heart in the region of a single fascicle can produce either **anterior hemiblock** or **posterior hemiblock.** It is possible to have bifascicular block in which anterior or posterior hemiblock is combined with right bundle branch block. The ECG features of hemiblock can be found in Table 1.

Table 1
ECG Criteria Diagnostic of Hemiblock Syndromes

Anterior Hemiblock	Posterior Hemiblock
Left axis deviation	Right axis deviation
Q waves in lead I	Q waves in lead III
Wide or deep S wave in lead V_6	Wide or deep S wave in lead I

Step 5. Determine the QT Interval

The QT interval is the time between the beginning of the QRS complex and the end of the T wave. It represents the total time taken for ventricular depolarization and repolarization. The QT interval varies with the heart rate; hence, a **corrected QT (QT_c)** must be determined based on the **measured QT (QT_m)** and the length of the preceding RR interval in seconds. The QT_c is calculated using **Bazet's formula**:

$$QT_c = QT_m / \sqrt{\text{RR interval}}$$

A normal QT_c is between 0.35 s and 0.44 s in duration. Table 2 lists some common causes that can alter QT_c.

Table 2
Common Clinical Scenarios Associated with a Change in the QT_c Interval

Short QT_c (< 0.35 s)	Long QT_c (> 0.44 s)
Hypercalcemia	Hypocalcemia
Digitalis toxicity	Hypokalemia
	Hypomagnesemia
	Hypothermia
	Hypothyroidism
	QT-prolonging drugs
	Congenital QT prolongation

Step 6. Determine the QRS Axis

The QRS axis is the direction of the mean QRS vector. Using the limb leads, the position of the QRS axis in the frontal plane can be determined (a QRS axis can also be determined in the axial plane but this process is not described here).

To determine the position of the QRS axis in the frontal plane, consider leads I and aVF (Figure 17). Normally, the QRS complex is positive in both these leads, indicating that the QRS axis is positioned downward and leftward in the frontal plane. A negative QRS complex in lead I or lead aVF indicates right or left axis deviation, respectively. In extreme right axis deviation, the QRS complex is predominantly negative in both leads I and aVF. The mean QRS axis is found in the lead with the largest positive QRS complex. The QRS axis can also be found by determining the limb lead in which the QRS complex is **isoelectric** (i.e. the same magnitude on either side of the baseline) since the QRS axis will be perpendicular to this lead.

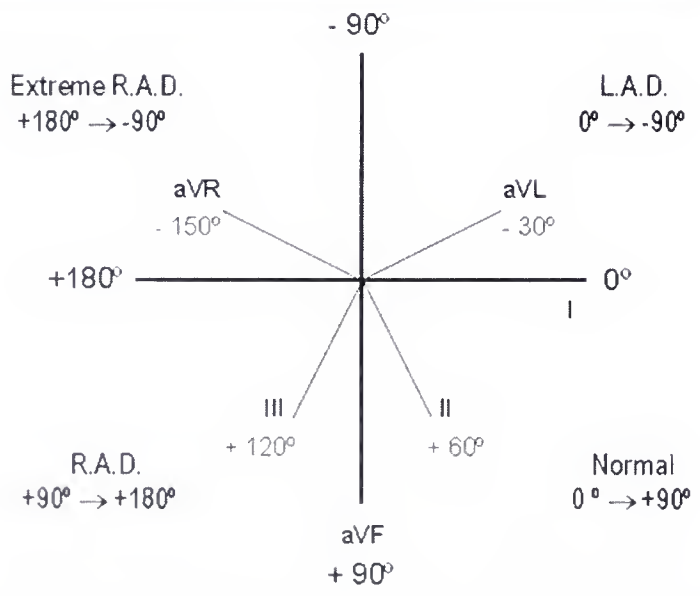

Figure 17. *Diagram of the frontal plane leads and their relationship to the mean QRS axis. When the QRS axis lies outside the lower left quadrant the axis is deviated. Left axis deviation occurs when the QRS axis is oriented at less than 0° while right axis deviation occurs when the QRS axis is oriented at greater than + 90°.*

Causes of axis deviation include changes in the physical position of the heart (pregnancy, lying down), left or right ventricular hypertrophy, left or right bundle branch block and infarction. Any axis deviation can therefore be informative in a variety of pathological conditions. The axis shifts toward hypertrophy and away from infarction.

Step 7. Look for Hypertrophy

Enlargement of the atria and ventricles occurs in heart diseases where the chambers must accommodate greater pressure and/or volume than they normally handle. Hypertrophy of a heart chamber is a chronic condition characterized by an increased thickness of the chamber wall. This is the response of the myocardium to an increased workload. Dilatation of the chamber often accompanies hypertrophy and its extent is dependent on the cause of the hypertrophy.

Left Atrial Hypertrophy (LAH). Left atrial overload is seen in mitral valve stenosis and insufficiency, acute myocardial infarction, left heart failure and left ventricular hypertrophy secondary to various causes. It is much more commonly identified on an ECG than right atrial hypertrophy. Since the P wave represents the contraction of both atria, atrial hypertrophy is evident in changes of the P wave. The characteristic ECG changes include (Figure 18):

- A broad positive P wave with duration greater than 0.12 s in any lead.
- A wide, notched P wave with two "humps" 0.04 s or more apart and the P mitrale in leads I, II, V_4-V_6.
- A biphasic P wave in which the terminal portion is large, wide and negative in lead V_1.

Right Atrial Hypertrophy (RAH). This condition is usually caused by right atrial overload and it is found in pulmonary valve stenosis, tricuspid valve stenosis and pulmonary hypertension (Figure 19).

- The result of right atrial hypertrophy can be detected by a P pulmonale – a tall, symmetrically peaked P wave (P ≥ 2.5 mm) seen in leads II, III, and aVF.
- Another characteristic change is a sharply peaked P wave in lead V_1.

Left Ventricular Hypertrophy (LVH). Left ventricular overload is the usual cause of left ventricular hypertrophy. It is seen in mitral insufficiency, aortic stenosis or insufficiency, systemic hypertension, acute MI, and hypertrophic cardiomyopathy. In this condition, the left ventricular wall is very thick, causing great QRS deflections (exaggerated height and depth) in the chest leads (Figure 20).

- The following changes in the R wave are often used to diagnose LVH: 1) R wave ≥ 15 mm in lead I; 2) R wave

≥ 11 mm in lead aVL; and 3) R wave ≥ 25 mm in lead V_5 or V_6.

- The following criteria of S wave changes are helpful: 1) S wave ≥ 15 mm in lead III; and 2) S wave ≥ 25 mm in lead V_1 or V_2.
- The sum of the height of the R waves and the depth of the S waves are often used to determine the presence of LVH.
- ***Limb leads:*** R(I) + S(III) ≥ 25 mm.
- ***Chest leads:*** S(V_1) + R(V_5) or (V_6) ≥ 35mm.
- QRS axis < –15°.
- ST segment depression of ≥ 1 mm is present in leads I, aVL, and V_5-V_6.
- T wave inversion is present in leads I, aVL, and V_5-V_6.
- The downward sloping ST segment along with the T wave inversion form a "strain" pattern of the QRS-ST-T complex seen in long-standing LVH.

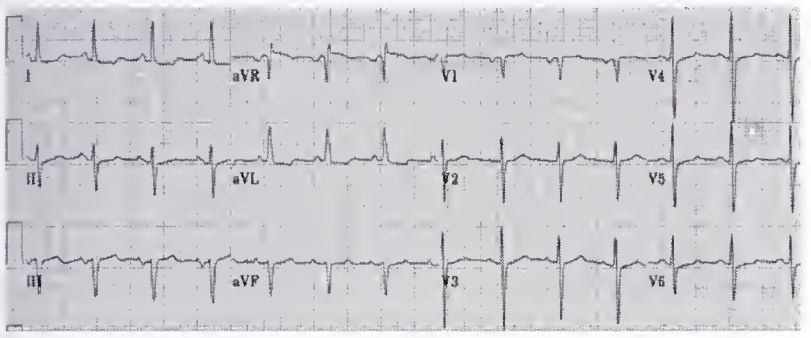

Figure 18. *Left atrial hypertrophy. Note the broad P wave, which appears notched in leads I, II, V_4, V_5 and V_6, and appears biphasic in leads V_1 and V_2.*

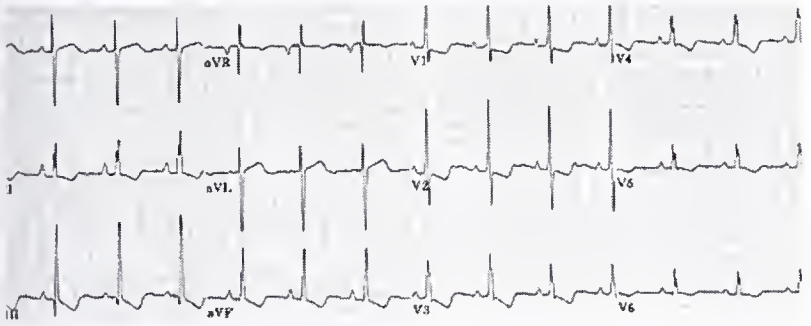

Figure 19. *Right atrial hypertrophy. The P wave is tall and peaked in leads II, III, V1 and aVF.*

Figure 20. *Left ventricular hypertrophy (LVH). See text for detailed information on the diagnosis of LVH. The S wave in V1 is deep and there is left axis deviation.*

Right Ventricular Hypertrophy (RVH). Right ventricular overload is found in pulmonary valve stenosis, congenital heart defects, tricuspid valve insufficiency, and pulmonary hypertension. A right axis deviation is usually present. Since the QRS complex represents ventricular activation, the abnormally large rightward electrical forces produced by right ventricular hypertrophy are reflected in the changes seen in the QRS complex (Figure 21).

- Normally in lead V_1, the QRS complex is mainly negative; however, in right ventricular hypertrophy, a large R wave (≥ 6 mm) is present in this lead (Table 3). The large R wave in V_1 decreases progressively in V_2-V_6.
- ST segment depression of ≥ 1 mm may be present in leads II, III, aVF, V_1, and sometimes in V_2 and V_3.
- T wave inversion is often present in leads V_1-V_3.
- The downward sloping ST segment along with the T wave inversion form a "strain" pattern of the QRS-ST-T complex also seen in long-standing RVH.

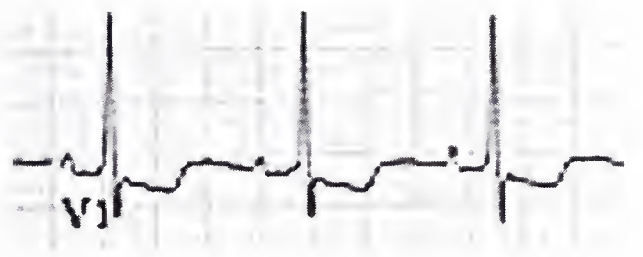

Figure 21. *Right ventricular hypertrophy (RVH). See text for detailed information on the diagnosis of RVH. The R wave in V_1 is tall and there is right axis deviation.*

Table 3
Differential Diagnosis of Tall R Wave in Lead V_1

- Posterior MI
- RVH
- Wolff-Parkinson-White Pre-Excitation
- Asymmetric Septal Hypertrophy (ASH)
- Right Bundle Branch Block
- Counterclockwise Rotation of the Heart

Step 8. Look for Changes in Acute MI

MI results from occlusion of a coronary artery. Following the occlusion, the myocardium progresses through various stages of impairment beginning with ischemia, proceeding to injury, and ending with infarction (tissue necrosis). There are specific changes in the ECG that will reflect these processes in the myocardium. The ECG of an acute MI, with its varying combination of ischemia, injury, and necrosis, is characterized by changes in the T wave, ST segment, and Q wave.

Inverted T waves. Ischemia is characterized by symmetrically inverted T waves that appear over the ischemic zone. They are due to a delay in the repolarization of the myocardium because of anoxia. Initially, during the reversible stages of injury, T waves may be tall and peaked or deeply inverted depending on the location of the ischemia. Ischemic T waves are upright in subendocardial ischemia whereas they are inverted in epicardial ischemia. As the ischemia progresses to the irreversible stage of necrosis T waves become deeply inverted.

ST segment elevation. Myocardial injury is characterized by downward concave ST segment elevation (≥ 1mm above base-

The presence of ST elevation indicates that the injury of the infarct is acute and usually indicates transmural involvement. ST segments are elevated in the leads facing the zone of injury and depressed in the opposite leads. Following the injury phase, as the MI progresses, the injured myocardium becomes necrotic and the current generated from the injury disappears as the tissue becomes electrically inert. The ST segment elevation begins to diminish and return to baseline. Other causes of ST elevation include: coronary vasospasm, acute pericarditis, and ventricular aneurysm.

ST depression. ST depression is a sign of severe myocardial ischemia (≥ 1 mm below baseline). This ECG change usually appears during the first hour following the onset of subendocardial MI, during an angina attack, or following exercise. The ST segments are depressed in the leads facing the ischemic tissue and are elevated in the opposite leads. Downward sloping ST segments are most specific for myocardial ischemia. Other common causes of ST depression include: LVH, RVH, LBBB, RBBB, and digitalis use.

Abnormal Q waves. The Q wave is the first negative deflection of the QRS complex and it may be normal or abnormal during an acute MI. Normal Q waves result from the depolarization of the interventricular septum from left to right. This small electrical force is the first step in the depolarization of the ventricles. The resultant **"septal" Q wave** is < 0.04 s wide and has a depth of < 25% of the height of the following R wave. Septal Q waves are commonly present in leads I, V_2, V_3, and V_6. Abnormal (significant) Q waves make the diagnosis of infarction. They denote irreversible myocardial necrosis in acute MI. A Q wave is abnormal if it is **≥ 0.04s** wide and has a depth of **≥ 25%** of the height of the succeeding R wave. Significant Q waves usually appear in the facing leads directly over necrotic, infarcted myocardial tissue. To detect an infarction, all the leads (except lead aVR) in the ECG tracing should be scanned for any significant Q waves.

Typical Patterns of Q Wave and Non-Q Wave MI

Acute Q wave MI occurs in approximately 50 to 70% of patients with acute MI. The typical pattern of **Q wave MI** in the facing ECG leads include:

- An initial symmetrically wide, deeply inverted or tall, peaked T wave within seconds of the onset of the acute MI.
- ST segment elevation within 20 to 40 minutes.
- Abnormal Q waves at about 2 hours.
- Return of ST elevation to baseline and appearance of symmetrically deep inverted T waves.

Characteristic changes seen in a **non-Q wave MI** in the facing ECG leads include:

- Evidence of symmetrically wide, inverted, or tall T waves within seconds of the onset.
- Elevation or depression of ST segment within about 30 minutes.
- Return of ST segments to baseline and appearance of symmetrically inverted T waves.
- No appearance of abnormal Q waves.

These ECG changes and the leads in which they appear depend on: 1) the location of the MI; 2) the extent of the specific myocardial wall involvement; and 3) the period that elapsed between the initial onset of the acute MI and the time the ECG was taken.

> When reading an ECG tracing, one should take note of the leads in which abnormal Q waves, ST segment elevation, and inverted T waves are present.

Since prognosis of an MI depends on its location, it is crucial to establish the site of infarction (Table 4).

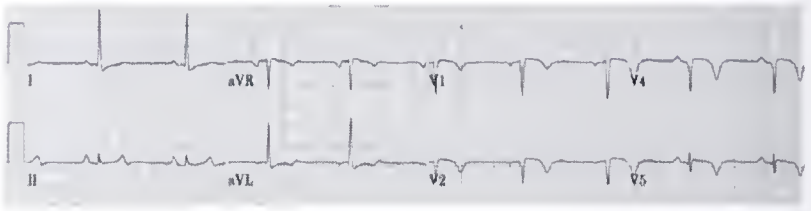

Figure 22. *Acute anterior myocardial infarction. In this example, the most prominent features are elevations of the ST segment and inversions of the T wave in leads V_2 through V_5. Q waves are seen but are somewhat difficult to appreciate in this case. The leads in which these changes occur determine the location of the infarction (see text and Table 4).*

Table 4
Localization of Acute Myocardial Infarction

LOCATION OF MI	LEADS
Anteroseptal	V_1, V_2
Anterior	V_2-V_5
Anterolateral	V_5-V_6
High Lateral	I, aVL
Inferior	II, III, aVF
Inferolateral	II, III, aVF, V_5, V_6
Posterior	V_1
Posterolateral	I, aVL, V_5, V_6

Step 9: Consider Effects of Electrolytes, Drugs and Other Events

Common clinical situations that produce characteristic ECG patterns are discussed below:

Hyperkalemia. Elevated serum potassium "tents" the T wave, widens the QRS complex and flattens the P wave. In extreme hyperkalemia, the P wave cannot be detected, and the QRS is extremely wide.

Hypokalemia. Hypokalemia produces a positive deflection on the tracing that occurs following the T wave known as **U wave**. With increasing severity of hypokalemia, the U wave becomes increasingly prominent and the T wave flattens out and may become inverted.

Hypercalcemia. Hypercalcemia shortens the QT interval while **hypocalcemia** lengthens it. Disordered serum calcium (or potassium) concentrations can lead to the development of dangerous arrhythmias.

Digitalis. Digitalis causes prolongation of the PR interval over 0.2 s, depression of the ST segment with a unique "scooped

out" appearance, flattened T waves, and shorter than normal QT intervals. When given in excess, digitalis causes SA block, paroxysmal atrial tachycardia with block, AV blocks, and tachycardia with AV dissociation. **Digitalis toxicity** stimulates ectopic discharge, leading to arrhythmias such as premature ventricular contractions, bigeminy, trigeminy, ventricular tachycardia, ventricular fibrillation, and atrial fibrillation.

Quinidine. Quinidine administered within therapeutic range produces ECG changes which include notching of a widened P wave, widening of the QRS complexes (> 0.12 s), ST depression, prolonged QT interval, and the presence of U waves. **Quinidine toxicity** causes a number of excitatory or inhibitory effects on the heart and its electrical conduction system. Such effects include premature ventricular contractions, ventricular tachycardia in the form of Torsade de Pointes, ventricular fibrillation, depression of myocardial contractility, SA block, AV block, and ventricular asystole.

Pulmonary embolism. A pulmonary embolus leads to pulmonary arterial hypertension resulting in cor pulmonale. The ECG changes include a large S wave in lead I (indicative of right axis deviation), and Q waves and inverted T waves in lead III. In addition, T wave inversion may be observed in the right chest leads. Right bundle branch block may also be seen.

Conclusion

Once the ECG has been studied completely, a diagnosis can be made and further investigations or interventions can be selected as necessary. For reference, some ECG changes that occur in a variety of disease states are listed in Table 5. Using the 9 steps described above, most ECG abnormalities seen in the clinical setting will be detected.

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Table 5
Summary of Various ECG Changes and Causes

ECG Portion	Change	Some Causes
P wave	Broad, > 0.12 s in any lead; notched in I, II, V_4, V_5 or V_6; biphasic in V_1 or V_2	Left atrial hypertrophy (P mitrale)
	Tall (≥ 2.5 mm) in leads II, III and aVF; peaked in V_1	Right atrial hypertrophy (P pulmonale)
PR interval	Long (> 0.20 s)	First degree block
	Short (< 0.12 s)	Accessory pathway (WPW or LGL syndromes)
Q wave	Wide (0.04 s) or prominent (1/3 QRS magnitude)	Old or acute infarction
QRS complex	Wide (> 0.08 s)	If < 0.12 s, hemiblock If > 0.12 s, bundle branch block or wide complex tachycardia (i.e. PVB, ventricular tachycardia)
	Tall (≥ 25 mm in V_5 or V_6) with left axis deviation and asymmetric T wave inversion	Left ventricular hypertrophy
	Tall (R ≥ 6 mm) in V_1 with right axis deviation	Right ventricular hypertrophy
QTc interval	Short (< 0.35 s)	Hypercalcemia or digitalis toxicity (the latter is also associated with T wave inversion)
	Long (> 0.43 s)	See Table 2
ST segment	Deviation from baseline in same direction as QRS (elevation)	Infarction (leads determine location)
	Deviation from baseline opposite to direction of QRS (depression)	Ischemia (leads determine location) or subendocardial infarction
T wave	Peaked	Hyperkalemia
	Flattened	Hypokalemia
	Symmetrically inverted	Ischemia or digitalis toxicity
	Asymmetrically inverted	Left ventricular hypertrophy
U wave	Present	Hypokalemia (but may be present in normal individuals)

Evidence-Based Medicine

A Primer on Medical Statistics – *P* Values and Confidence Intervals

Evette Weil, B.A. (OT2)

Introduction

This article is a continuation of the evidence-based medicine series that began in the May 1999 issue of the UTMJ. Evidence-based medicine requires that the physician have a fundamental understanding of statistical concepts in order to critically interpret the published literature. This and future articles in the next two issues of the UTMJ are intended to serve as an introductory primer on statistics relevant to the clinician. This article starts with the most basic measures used in clinical epidemiology, p values and confidence intervals, measures that are likely to be familiar to most readers. Future articles will examine in detail other statistical concepts, such as odds ratios, risk reduction, number needed to treat, correlation, and regression.

Case Study

Fibrate therapy of low HDL levels reduces major cardiovascular events

This study investigated the use of a fibrate, gemfibrozil, in the secondary prevention of coronary heart disease in men with low levels of high density lipoprotein (HDL) cholesterol. In a double-blind trial, 2531 men with coronary artery disease and a primary lipid disorder of low HDL levels were randomized to gemfibrozil therapy or placebo. Patients had normal or low triglyceride and low density lipoprotein (LDL) levels. At one year, HDL cholesterol was increased by 6%, triglycerides were decreased by 31%, and LDL cholesterol did not change. A primary event, defined as myocardial infarction or death from coronary causes, occurred in 17.3% of the gemfibrozil group and in 21.7% of the placebo group. The relative risk reduction was 22% (95% confidence interval: 7 to 35%; p=0.006). There was no significant difference in rates of coronary revascularization, hospitalization for unstable angina, death from any cause, and cancer. This study suggests that fibrate therapy may have a role in the treatment of patients with coronary artery disease and low levels of HDL.

Source: Rubins *et al.* (1999). *NEJM.* 341:410-418

1. Significance

1.1 The Importance of Chance

Statistical analysis of a clinical trial assumes that there is a true treatment effect, but that the trial can only estimate that effect. There is always the possibility that an apparently large effect found in a particular sample is due to chance. This notion of chance is integral to all statistical measures.

The conventional model for explaining the idea of chance is a coin-toss experiment. We can intuitively understand that on any given coin toss there is a 50% chance that the result will be heads. However, we can imagine a scenario of a fair coin being tossed 10 times will result in 7 heads and 3 tails. The divergence from the 50:50 ratio is due to chance. Likewise, in a clinical trial testing the efficacy of a new drug, the true benefit of the drug may be a 50% reduction in mortality, but the amount measured may be 30% or 70%. This potential variation complicates our ability to judge the validity and applicability of the results.

Let us return to our coin toss experiment. We may accept that in an unbiased test, 7 heads may result from 10 coin tosses. However, if we tossed the coin 10 times, and heads came up 9 times, it would be more difficult to ascribe the results simply to chance. Similarly, we would be less ready to accept that 70 out of 100 or 700 out of 1000 coin tosses could be due to chance.

With these results, we would suspect that there were some external factor favouring the heads side of the coin. These two examples demonstrate that the likelihood of a given result being real, as opposed to chance, is dependent on the magnitude of the outcome and the number of independent observations (sample size).

1.2 P Values

The variation between real and random findings may be represented statistically with *p* values. **A *p* value is the probability that a given result occurred by chance.** Using our coin toss experiment, we can calculate with a statistical formula (binomial expansion) the chance of obtaining at least 7 heads in 10 coin tosses. This number is the *p* value of the experiment. For 10 coin tosses, the probability of seeing 7 or more heads (or the same arrangement with tails) is calculated to be 17%. In other words, in 17 out of 100 experiments, we would expect to see at least 7 heads or 7 tails; so p=0.17.

Now imagine, instead of a coin toss, a clinical experiment where 7 out of 10 patients experienced a favourable outcome, and a statistical test generates a p value of 0.17. This means that there is a 17% probability that the observed result is merely due to chance. The question now becomes one of clinical rather than statistical judgement: Do we consider a result with such a *p* value to be significant?

For most scientific literature, the arbitrary line drawn between a significant and non-significant finding is $p < 0.05$. This implies that the medical profession considers a result noteworthy if the odds are less than 1 in 20 that the result is due to chance. Highly significant results are $p < 0.01$ or odds of 1 in 100 that the result is due to chance.[1]

We can illustrate the use of significance with the clinical trial described above. In this trial, researchers compared a drug, gemfibrozil, to placebo for the secondary prevention of coronary events in patients with low HDL cholesterol.[2] The primary outcome for the study was nonfatal myocardial infarction or death from coronary causes. The study found that 17.3% of patients given gemfibrozil had a primary event versus 21.7% of patients given placebo. This represents a 22% reduction in risk. More importantly, this reduction has a *p* value of 0.006, and is, therefore, highly significant. (Note: More comprehensive explanations of risk reduction will be given in the next article in this series).

The gemfibrozil study had as a secondary outcome death from any cause. In this case, 15.7% of patients given gemfibrozil died compared to 17.4% of those given placebo. This represents an 11% reduction in risk. However, the associated *p* value is only 0.23, and is considered non-significant. How are we to understand these figures? We cannot interpret this as proving that gemfibrozil had no effect on overall mortality. We can only say that the study was not large enough – or, in epidemiological jargon, did not have enough power – to determine whether or not gemfibrozil had an effect on death from any cause.

1.3 Multiple Outcomes

The fact that the gemfibrozil study tested multiple outcomes (one primary and 9 secondary) brings up a prevalent problem in the medical literature. When testing for multiple outcomes, there is an increased likelihood that a particular result is due to chance. If we have 10 outcomes, each with an individual *p* value of 0.05 (i.e. 95% chance that the result is valid and not merely due to chance), the probability that all 10 of them simultaneously are valid is $(0.95)^{10} = 0.60$. In other words, there is a 40% probability that at least one of the 10 results is due to chance despite the individual *p* values of 0.05. A more comprehensive explanation of this phenomenon is given by Guyatt *et al.*[3]

From a practical point of view, this means that with multiple endpoints we have to reduce our threshold for significance to compensate for the fact that more of our results can be ascribed to chance. One simple strategy for managing this problem – the one used in gemfibrozil study – is to distinguish between a single primary outcome and multiple secondary outcomes. The standard *p* value threshold of 0.05 can be applied to the primary outcome. Therefore, the lower incidence of the primary outcome of myocardial infarction or death from coronary heart disease, $p = 0.006$, remains significant. For the multiple secondary outcomes, the threshold *p* value is divided by the number of measured outcomes. In this case, the new threshold becomes 0.05 divided by 9 or 0.006. Now we can even make a stronger case that the lower incidence of the secondary outcome of death from any cause, $p = 0.23$, is not significant.

2. Confidence Intervals

2.1 An Additional Way to Report Results

The concept that measured results may be due either to a real effect or to chance can also be expressed statistically with confidence intervals (CI). In reports of clinical trials, a single result (point estimate) is often given with both a *p* value and a confidence interval. **A confidence interval relates the point estimate of a given parameter to the true population parameter.** In other words, a 95% CI means that there is a 95% probability that the true value lies in the given range, assuming a normal distribution. Strictly speaking, a 95% confidence interval means that if the study were repeated 100 times and CI's constructed in the same way, 95% of these CI's would contain the true value. The first definition is more comprehensible, but statisticians dislike it, because it implies that the true value is changing. CI's gives a range of included and excluded values on which to base clinical decisions in the face of uncertainty.

In the case study, the point estimate for the reduction in nonfatal myocardial infarction or death due to coronary heart disease is 22% for gemfibrozil versus placebo. The authors also report that the 95% confidence interval for this measure is 7 to 35% risk reduction. This means that we can be 95% confident that the *true* risk reduction would lie in this range. Since the lowest limit of this range, +7, is still above zero, the authors can be

confident that even their most conservative estimate shows benefit from gemfibrozil.

In contrast, the confidence interval for relative risk reduction of death from any cause ranges from –8 to 27%. The negative value means that at the lower limit, gemfibrozil may actually increase the all cause mortality risk. How can we interpret these figures? Our point estimate, 11% risk reduction with gemfibrozil, is our best single estimate of the true outcome. All of the other values in the confidence interval distribute normally around the point estimate. We can conclude that this study showed a trend toward risk reduction, but it is not definitive, because the lower limit of our confidence interval includes the possibility that the drug actually increases all-cause mortality.

2.2 The value of confidence intervals

Confidence intervals are particularly useful because they allow the reader to determine whether a study was large enough. As the sample size of a study increases, the confidence interval becomes narrower, since, as was noted above, with more "tries" fewer results can be attributed to chance. So with a small study, we are likely to obtain a large confidence interval with greater likelihood that the two limits would fall on either side of a threshold value.

The threshold value depends on the nature of the trial and on clinical judgement. A larger study will always give a narrower CI, but is it worthwhile to do a larger trial? Consider a highly toxic drug used to treat some non-life threatening condition. Suppose the first trial showed a 4% improvement in symptoms with a CI of –2% to 10%. The upper confidence limit suggests that the real benefit is unlikely to be greater than a 10% improvement, and we might say that such a benefit "isn't worth it" since the drug is so toxic. Clearly we are now describing clinical significance rather than statistical significance. In contrast, in the gemfibrozil study, the upper confidence limit suggested that the benefit might be as high as a 27% relative reduction in all-cause mortality, something that may well be clinically important. Researchers and clinicians need to decide where to place the threshold; deciding, for example, that only a risk reduction greater than 5% would merit a change in practice.

In general, the rules for interpreting confidence intervals are as follows: 1) For a trial that appears to be positive, if the lower limit is above the threshold of what would be considered a clinically important effect, the study is positive and definitive; 2) for a trial that appears positive, but the lower limit is below the threshold, the study is likely to be positive, but is not definitive; likewise, 3) for a trial that appears negative, but the upper limit of the confidence interval is above the threshold, the study is likely to be negative, but is not definitive; and finally, 4) for a trial that appears to be negative and the upper limit is below the threshold, the results can be viewed as definitively negative (Table 1).

Table 1
Rules for Interpreting Confidence Intervals

Consider a situation where a 10% improvement in symptoms is required in order to justify the use of the therapy.

Result: % change in symptoms (95% CI)	Classification	Interpretation
27% (15%, 42%)	Positive and definitive	Positive because the CI does not include zero and definitive because the lower CI is greater than our clinical threshold of 10%
14% (2%, 28%)	Positive but not definitive	Not definitive because the lower CI is less than our clinical threshold of 10%
–3% (-12%, 15%)	Negative but not definitive	Negative because the CI crosses zero, but not definitive because the upper CI includes the possibility of clinically significant benefit
–1% (-6%, 8%)	Negative and definitive	Negative because the CI crosses zero and definitive because upper CI is below our clinical threshold of 10%

Conclusion

The concepts of *p* values and confidence intervals highlight the point that results reported from clinical trials are only estimates of the *true* effect of the intervention. *P* values and confidence intervals allow the physician to read an article and make a reasonable decision after regarding the validity of the results. It is this judgement that prompts the physician to consider altering his or her practices, and, therefore, represents the fundamental step in practicing evidence-based medicine.

Acknowledgments

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Chest Pain: An Unusual Suspect

Sharon J. Kular, B.Sc. (0T2), Jordana B. Sacks, B.Sc. (0T2), and Wayne L. Gold, M.D., F.R.C.P.(C)*

Introducing Morning Report

Morning Report is a traditional round in most internal medicine training programmes. While the specific format of Morning Report varies between institutions, it typically involves the presentation of a clinical case followed by a case-oriented discussion. At the University of Toronto, the goals of Morning Report are to facilitate teaching and learning at various levels of medical training, to promote social interaction between the medical faculty and the medical housestaff, and to discuss issues related to local hospital structure and function. Traditionally, the medical team that was on-call the night prior to Morning Report presents a clinical case from the previous day's admissions. A staff physician then leads a discussion of the case with the goal of emphasizing the clinical reasoning process involved in the diagnosis and management of the patient's condition. Discussion focuses on the generation of a provisional and differential diagnosis for the presenting complaint, refinement of the provisional diagnosis as additional information becomes available, the anticipation of laboratory and radiological findings, and principles of management of the condition.

The Scene

In a conference room in a University of Toronto teaching hospital, medical students, residents, and staff physicians are seated around a conference table. Rita, a third year medical student, Monica, a fourth year medical student, and Erica, a second year resident in internal medicine (PGY-2) have worked overnight admitting patients to the clinical teaching units. They have selected one case from the previous night's admissions that will be presented for discussion. Dr. Bega, a staff internist, will facilitate a discussion of the case.

Rita: Mrs. T. is a 42-year-old woman who presented to the emergency department with the chief complaint of right-sided chest pain of five weeks' duration.

Dr. Bega: Let's pause for a moment. Clinicians usually begin to formulate a differential diagnosis after hearing the patient's chief complaint. Monica, what are some of the diagnostic possibilities that come to mind when you hear the chief complaint of chest pain?

Monica: I generally approach the symptom of chest pain by considering four major categories of disease: cardiac disease, pulmonary disease, gastrointestinal causes of chest pain, and chest pain related to abnormalities of the chest wall. Cardiac causes of chest pain include angina and myocardial infarction, pericarditis, and aortic dissection. Pulmonary causes of chest pain include pulmonary thromboembolism, pneumonia with involvement of the pleura, other pleural diseases including viral pleurisy and pneumothorax, and thoracic tumours. Gastrointestinal causes of chest pain include gastroesophageal reflux disease, diffuse esophageal spasm, peptic ulcer disease, and biliary tract disease including acute cholecystitis. Chest wall diseases causing chest pain include trauma, with or without rib fracture, and nerve root inflammation which occurs in herpes zoster. Chest pain may also be a feature of panic attacks.

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Dr. Bega: Monica, that is an excellent approach. Erica, since the differential diagnosis is so extensive, what additional information would you like to obtain on history?

Erica: Since the patient's chief complaint was chest pain, I would like to have more information regarding the features of the pain. Specifically, I would like the following information: the onset, chronology, and duration of the pain; location and radiation of the pain; intensity of the pain on a severity scale out of ten (0 = no pain; 10 = the worst pain that the patient has ever experienced); and precipitating and/or alleviating factors. Importantly, any symptom should be interpreted in the context of what is known about the patient's past medical history. I am also interested in knowing if the patient has experienced any associated symptoms and whether there are risk factors for any of the causes of chest pain that we have already mentioned.

Dr. Bega: Rita, can you provide us with more information about the pain?

Rita: The history dates back five weeks ago when the patient began to experience right-sided chest pain which worsened with inspiration. She was seen by her family physician and was prescribed a non-steroidal anti-inflammatory agent for presumed musculoskeletal chest wall pain. There was no relief of her symptoms with this medication. At that time, there were no other associated symptoms. However, three weeks prior to her presentation to the emergency department, the patient developed a productive cough that also exacerbated her pain. At the same time, she began to experience fever and chills, so she returned to her family physician's office. A chest radiograph was performed which showed opacification of the right lower lobe with the presence of air bronchograms. She was prescribed cefaclor for a presumptive diagnosis of community-acquired pneumonia. Despite three weeks of empiric antimicrobial therapy, her symptoms persisted and worsened. Over that time, she developed drenching night sweats and also experienced an involuntary 5 kg weight loss. On further inquiry, she has a 40-pack-year smoking history. She denies hemoptysis. She had no known tuberculous contacts. There has been no recent travel and no animal exposures. There was no history of prolonged immobilization or leg swelling to suggest a diagnosis of pulmonary thromboembolism and there was no history of recent trauma to the chest wall. There was no history of diabetes, hypertension, or dyslipidemia and there was no family history of coronary artery disease.

Dr. Bega: Thank you, Rita. Why don't we pause here for a moment. Erica, what are your thoughts at this moment?

Erica: The patient has experienced fever, a productive cough, and pleuritic chest pain. There has been associated weight loss. The description of the chest radiograph is consistent with lung consolidation. The historical and radiographic features are suggestive of a diagnosis of community-acquired pneumonia. The pleuritic chest pain is compatible with pleural involvement and suggests the possibility of an associated parapneumonic effusion. The lack of response to antimicrobial therapy can indicate a number of possibilities: the infecting organism may not be responsive to the antibiotic that was selected; there may be an undrained focus of infection such as an empyema; or we may be dealing with another diagnosis. The patient has a 40-pack-year smoking history. This raises concern about a lung malignancy. Also, the history of pleuritic chest pain should always raise the possibility of a diagnosis of pulmonary thromboembolism. I would like to hear about the patient's physical examination.

Rita: On general inspection, the patient appeared unwell. She was diaphoretic. Blood pressure was 110/70 mmHg; heart rate was 110/minute and regular; respiratory rate was 22 breaths/minute. Pulse oximetry revealed an oxygen saturation of 86% on room air. Oropharyngeal examination revealed carious dentition. The JVP was 2 cm above the sternal angle. Cardiovascular examination showed normal heart sounds; there were no murmurs. Chest examination revealed dullness to percussion in the right lung base. There was a decrease in tactile fremitus compared to the left side. Auscultation revealed decreased air entry in the right lung base. Bronchial breath sounds were heard above the level of percussion dullness. Abdominal and central nervous system examinations were normal.

Dr. Bega: Monica, how do you interpret the findings of the chest examination?

Monica: The findings of dullness to percussion in the right lung base, with the associated findings of a decrease in tactile fremitus and decreased air entry, are compatible with the clinical features of a pleural effusion. You may hear bronchial breath sounds just above the level of a pleural effusion.

Dr. Bega: Very good. Rita, how do these findings differ from the findings that you would expect with lung consolidation?

Rita: In both consolidation and pleural effusion, you expect to find dullness to percussion. However, in consolidation you would expect to find an increase in tactile fremitus as airway sounds are more readily transmitted to the chest wall through consolidated lung tissue. Conversely, in a pleural effusion there is accumulation of fluid in the pleural space. This diminishes the transmission of airway sounds to the chest wall and results in a decrease in tactile fremitus. You would also expect to hear bronchial breath sounds in the setting of consolidation. Additionally, you may elicit the findings of egophony and whispering pectoriloquy in the presence of consolidation (Table 1).

Table 1
Physical Examination Features of Consolidation and Pleural Effusions

	Consolidation	Pleural effusion
Percussion note:	Dull over the area of consolidation	Dull to flat over the fluid
Breath sounds:	Bronchial	Decreased to absent
Tactile fremitus:	Increased	Decreased to absent
Transmitted voice sounds:	Bronchophony; egophony; and whispered pectoriloquy	None
Adventitious sounds:	Late inspiratory crackles	None, except a possible pleural rub

Adapted from: Bates B, Bickely LS, and Hoekelman RA. A Guide to Physical Examination and History Taking, 6th Edition. J. B. Lippincott Company: Philadelphia, pp. 256-257.

Dr. Bega: Rita, do we have a chest radiograph to review?

Rita: Yes. The chest radiograph revealed a large right-sided pleural effusion. The underlying lung parenchyma was poorly visualized (Figure 1).

Figure 1. *Chest radiograph demonstrating right pleural effusion.*

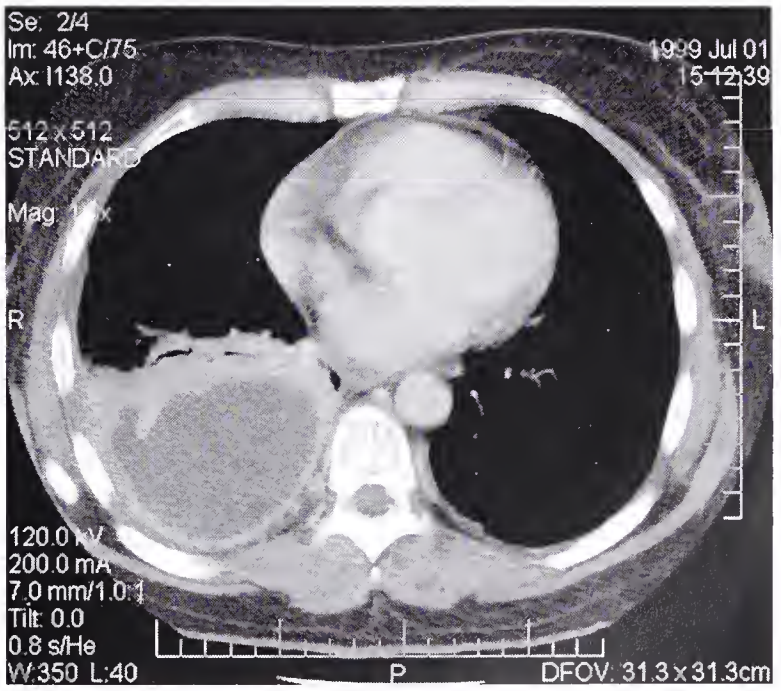

Figure 2. *Computed tomogram of the thorax revealing a large, right-sided pleural effusion. Adjacent to the fluid collection is an atelectatic lung*

Dr. Bega: Erica, do the findings of the physical examination and chest radiograph support your initial clinical impression?

Erica. Yes. There is a large right-sided pleural effusion. The patient has experienced fever and a productive cough that has not been responsive to empiric antimicrobial therapy. The most likely diagnosis remains an undrained focus of infection in the pleural space (empyema) which is likely secondary to a contiguous pneumonia.

Dr. Bega: Erica, what additional investigations would you like to order?

Erica: I would order a complete blood cell count (CBC) and differential, serum electrolytes and creatinine, and blood urea nitrogen. I would also perform a diagnostic thoracentesis after ensuring that there are no coagulation abnormalities.

Dr. Bega: Rita, do we have the results of these investigations?

Rita: Yes. The complete blood count revealed a hemoglobin concentration of 98.0 g/L with an MCV of 82.1 fL. The white blood cell count (WBC) was 16.4 X 10^9/L; the polymorphonuclear count was 13.2 X 10^9/L with the presence of toxic granulations. The serum electrolytes, creatinine, blood urea nitrogen, and INR were normal. An electrocardiogram was also ordered which was normal.

Dr. Bega: Monica, how do you interpret the results of the CBC?

Monica: The patient has a normocytic anemia that is compatible with the diagnosis of an anemia of chronic inflammation. As well, there is a leukocytosis with neutrophilia that is compatible with the presence of an infection.

Dr. Bega: Do we have the results of the pleural fluid analysis?

Rita: Yes (Table 2).

Dr. Bega: Erica, could you please interpret these results for us?

Erica: Pleural effusions are characterized as either transudative or exudative based on their biochemical profile. A transudative pleural effusion occurs when systemic factors that influence the formation and absorption of the pleural fluid are altered. The three most common causes of transudative pleural effusions are congestive heart failure, cirrhosis, and nephrotic syndrome. Exudative pleural effusions occur when local factors that influence the formation and absorption of pleural fluid are altered. Principle causes of exudative pleural effusions include parapneumonic effusions, malignant pleural effusions, viral pleurisy, pulmonary thromboembolism, and connective tissue diseases (Table 3).

Table 2
Pleural Fluid (PF) Analysis

PF protein	43 g/L
serum protein	72 g/L
PF/serum protein	0.6
PF LDH*	4330 U/L
serum LDH	150 U/L
PF/serum LDH	29
PF glucose	2.6 mmol/L
pH	7.06
WBC	9400 x 10^9/L
Cytology	No malignant cells
Gram stain	Numerous gram-positive cocci in chains; numerous gram-negative bacilli

LDH = lactate dehydrogenase

Table 3
Differential Diagnoses of Pleural Effusions

TRANSDATIVE PLEURAL EFFUSIONS
A. Congestive Heart Failure
B. Cirrhosis
C. Nephrotic Syndrome
D. Myxedema
E. Pericardial Disease

EXUDATIVE PLEURAL EFFUSIONS
A. Neoplastic diseases
    1. Metastatic disease
    2. Mesothelioma
B. Infectious Diseases
    1. Bacterial infections
    2. Tuberculosis
    3. Fungal infections
C. Gastrointestinal diseases
    1. Intraabdominal abscesses
    2. Pancreatitis
D. Collagen-vascular diseases
    1. Rheumatoid arthritis
    2. Systemic lupus erythematosus
E. Uremia
F. Drug-induced pleural disease

To be classified as an exudative pleural effusion, at least one of the following criteria must be met: 1) PF/serum protein > 0.5; 2) PF/serum LDH > 0.6; and 3) PF LDH > 2/3 upper normal serum limit (< 190 U/L). If none of these conditions are met, the effusion is characterized as a transudative pleural effusion. The treatment of a transudative pleural effusion is the treatment of the underlying systemic disease.

This patient has an exudative pleural effusion. The presence of numerous pus cells and micro-organisms on Gram staining indicates the presence of an empyema. Indications for chest tube drainage include: 1) the presence of gross pus in the pleural space; 2) visible organisms on Gram staining of the pleural fluid; 3) pleural fluid glucose level of less than 2.8 mmol/L; and 4) pleural fluid pH below 7.00.

This patient's pleural effusion requires chest tube drainage in addition to the administration of intravenous antimicrobial therapy. The presence of both Gram-positive cocci and Gram-negative bacilli on Gram staining suggests a mixed anaerobic pleuropulmonary infection. We elected to initiate therapy with intravenous penicillin 4.0 X 10^6 U every 6 hrs and oral metronidazole 500 mg p.o. tid. A chest tube was also inserted.

Dr. Bega: Excellent. Were any other investigations performed?

Rita: Yes. A computed tomogram of the thorax was requested (Figure 2). It revealed the large right pleural effusion. Adjacent to the effusion, there were areas of lung consolidation. There were no lung nodules or enlarged lymph nodes. The airways appeared normal.

Dr. Bega: Thank you Rita. That was an excellent presentation of a very interesting case. I look forward to receiving follow-up on this case.

Follow-up: Culture of the pleural fluid grew *Peptostreptococcus* magnus and a *Fusobacterium species*. The chest tube was removed on the fifth day of hospital admission. The patient received a 2-week course of parenteral antibiotic therapy followed by a 2-week course of amoxicillin/clavulanate 500/125 mg p.o. tid. A repeat CBC revealed a resolution of the anemia. The patient has quit smoking. Pneumococcal vaccination and yearly influenza vaccinations were recommended.

Clinical Pearls

1. In cases of community-acquired pneumonia, the median time to resolution of fever is 2 to 3 days.
2. Persistence of fever beyond this time requires prompt, careful clinical re-evaluation.
3. Causes of persistent fever include resistance of the infecting organism to the selected antimicrobial agent(s) or the presence of a persistent undrained focus of inflammation such as a parapneumonic effusion.
4. In cases of parapneumonic effusion, a diagnostic thoracentesis should be performed in order to determine if chest tube drainage is required.
5. Chest tube drainage is required for the management of complicated parapneumonic effusions:
   i. The presence of gross pus in the pleural space.
   ii. Visible micro-organisms on Gram staining of the pleural fluid.
   iii. Pleural fluid glucose level of less than 2.8 mmol/L.
   iv. Pleural fluid pH below 7.00.
6. Chest pain is frequently the presenting complaint in patients with pleural disease.

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'Edema Everywhere'

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Case Presentation

A 58-year-old man with a history of Type 2 diabetes mellitus was admitted for the evaluation of gross, generalized edema (anasarca).

Seven months prior: The patient presented to his family physician with a petechial rash over the lower extremities. A skin biopsy was performed which demonstrated non-specific inflammation. The rash resolved upon treatment with a topical steroid ointment.

Four months prior: The patient developed leg ulcers, which were treated with prednisone 75 mg po bid for presumed lower extremity vasculitis. His steroid therapy was complicated by the development of generalized edema, including abdominal distention. His weight increased by 23 kg. Furosemide (40 mg po daily) was prescribed for the management of his edema and resulted in significant improvement.

Three months prior: The patient was admitted to hospital for the management of increasing peripheral edema, skin breakdown involving the lower extremities, and ascites. A number of laboratory and radiologic investigations were performed (Table 1). Prednisone was discontinued. Topical silver sulfadiazine ointment and occlusive dressings were applied to the lower extremity ulcers. With aggressive diuresis over a 7-day hospital stay, the patient's weight decreased from 92.1 kg to 78.1 kg. Discharge medications included Novolin 30/70 24 units sc bid, spironolactone 100 mg po daily, furosemide 80 mg po daily, atenolol 50 mg po daily, quinapril 20 mg po daily, and metformin 500 mg po tid. Home nursing care was arranged to help with the management of his ulcers.

Table 1
Laboratory Investigations Performed Three Months Prior to Current Admission

Variable	Value	Range
Sodium	133	135 - 145 mmol/L
Potassium	3.6	3.5 - 5.0 mmol/L
Chloride	91	95 - 108 mmol/L
Creatinine	144	40 - 130 µmol/L
Glucose	5.1	3.9 - 6.9 mmol/L
BUN	15.6	3.0 - 7.0 mmol/L
Hemoglobin	134	115 - 165 g/L
HbA1c	0.096	<0.06 of Total Hb
WBC count	8.2	3.5 – 12.0 x 10^9/L
Platelet count	26	150 - 450x10^{12}/L
PT	13.2	9 – 13 s
PTT	26.4	26 – 36 s
AST	60	< 40 U/L
LDH	886	50 - 240 U/L
ALP	161	35 - 110 U/L
Total Bilirubin	18	<18 mol/L
Albumin	26	35 - 50 g/L
Urine glucose	positive	negative
Urine protein	negative	negative
Abdominal Ultrasound	5-6 L ascitic fluid, liver poorly visualized, multiple gallstones, slight splenomegaly; kidneys 11.7cm (R) and 11.6 cm (L).	
2D-Echocardiogram and ECG	Grade II/ IV LV function with hypokinesia in apex and septum; normal sinus rhythm and rate; Q waves in V_1 through V_3; no ST segment or T wave abnormalities.	
CXR	Atelectasis in lung bases	

Two months prior: The patient was re-admitted to hospital on three separate occasions for the management of his recurrent ascites, edema, and diabetes. There was worsening of his renal function (creatinine = 233 mmol/L). The patient also complained of abdominal discomfort, generalized weakness, and fatigue. As part of the edema workup, he had an outpatient nephrology assessment. Urinalysis was normal: there was no proteinuria, no hematuria, and no urinary sediment. It was felt that renal disease was an unlikely cause for his anasarca.

He was subsequently admitted to a university-affiliated General Internal Medicine Clinical Teaching Unit.

Current admission: Inquiry into past medical history revealed significant alcohol consumption, 40 oz/week (~1180 g/week) of rum for 20 years, but he had been abstinent for the past 1.5 years. In addition, longstanding, poorly controlled Type 2 diabetes mellitus (DM) and associated complications, including renal insufficiency (creatinine range 140-200 mmol/L) and non-proliferative diabetic retinopathy, were revealed. Past medical history also included prior myocardial infarction, hypertension, and hyperlipidemia. There was no prior history of congestive heart failure or dyspnea.

Medications on admission included: Novolin 30/70 26 units sc bid, furosemide 80 mg po daily, spironolactone 100 mg po daily, nitroglycerine 0.3-0.6 mg sl prn, and oxazepam 30-60 mg hs prn.

At the time of admission, the patient was alert, oriented, and in no apparent distress. Vital signs were: heart rate 114 beats/minute, blood pressure 120/70 mmHg, and respiratory rate 18 breaths/min. Oxygen saturation was normal. JVP was 3 cm above the sternal angle. The patient was not in any respiratory distress. Chest examination revealed fine inspiratory bilateral crackles at the lung bases. Precordial examination revealed normal first and second heart sounds, with no extra sounds or murmurs. There was bilateral pitting edema to the ankles.

Abdominal examination revealed bulging flanks, with dullness to percussion at the flanks, 5 cm of shifting dullness, and a positive fluid wave. There was no palpable splenomegaly and Castell's sign was negative. There was no jaundice or scleral icterus. However, there were spider nevi present on the trunk, as well as loss of axillary hair bilaterally. No other peripheral stigmata of chronic liver disease were apparent.

Lower extremity leg ulcers were noted bilaterally. On the right side, there were multiple weeping ulcers with surrounding cellulitis with areas of tissue necrosis. Multiple ulcers were also observed on the left side. A number of laboratory investigations were performed (Table 2).

Table 2
Results of Laboratory Investigations at Current Admission

Variable	Value	Range
Sodium	133	135 – 145 mmol/L
Potassium	4.7	3.5 – 5.0 mmol/L
BUN	16.7	3.0 – 7.0 mmol/L
Chloride	97	95 – 108 mmol/L
Creatinine	189	40 – 130 mmol/L
Glucose (fasting)	10.7	< 6.1 mmol/L
Urate	817	Males: 238 – 506 µmol/L
Total Cholesterol	3.23	high ≤ 6.21 mmol/L
LDL	1.94	high ≤ 4.14 mmol/L
Triglycerides	1.17	< 2.26 mmol/L
Total Iron	9	4 – 30 ≤ mol/L
Transferrin	1.78	1.88 – 3.41 g/L
Iron saturation	0.21	0.12 – 0.57 %
TSH	5.39	0.50 – 4.7 mIU/L
HbA1c	.056	< 0.06
AST	34	< 40 U/L
ALT	38	< 40 U/L
LDH	718	50 – 240 U/L
ALP	417	35 – 110 U/L
Total Bilirubin	27	< 18 mol/L
Albumin	31	35 – 50 g/L
Hemoglobin	117	115 – 165 g/L
WBC count	9.3	3.5 – 12.0 x 10^9/L
Platelets	79	150 – 450 x 10^{12}/L
PT	17	9 – 13 s
PTT	42	26 – 36 s
INR	1.35	0.9 – 1.1
24 hour Urine Function (protein)	0.076	negligible
Abdominal Ultrasound	Coarse, nodular liver; small mobile calculi in gallbladder; kidneys: 9.8 cm (R) 10.1 cm (L); common bile duct not well seen; normal intrahepatic ducts; Doppler revealed normal flow and direction in hepatic veins	
2D-Echocardiogram and EKG	Grade II/IV LV function with hypokinesia in apex and septum; normal sinus rhythm and rate; Q waves in V_1 through V_3; reduced voltages	
Paracentesis	2.2 L cloudy fluid; WBC,400x10^6/L 96% lymphocytes, 4% neutrophils); RBC, 10, 000 x 10^6/L	
Cryocrit	Negative	
Immunoglobulin survey	Trivial spikes within polyclonal increases of IgG 20.3 mmol/L, IgA 9.34 mmol/L, IgM 2.7 mmol/L	
Blood Smear	Hypersegmentation of neutrophils (PMN)	
Viral Serology	Hepatitis B and C Negative	
Liver Biopsy	Moderate to severe alcoholic cirrhosis	

On day following admission, paracentesis was performed and 6.5 L of cloudy ascitic fluid was removed. Laboratory analysis of the ascitic fluid was performed and revealed the following: WBC, 437 x 10^6/L (5% PMN, 50% lymphocytes, 40% macrophages); albumin, 3 g/L; amylase, 12 U/L; LDH, 64 U/L; and protein, 17 g/L. Culture of the ascitic fluid was negative for bacteria. The serum/ascites albumin gradient was 28 g/L. In addition, an ultrasound-guided percutaneous liver biopsy was performed.

Compression therapy for the ulcers was initiated with 1:20 sodium hypochlorite compresses. The ulcers were debrided. A culture of the ulcers was negative. The patient's weight decreased from 89 kg to 73 kg over his 8 days of hospitalization.

In summary, the patient is a 58-year-old male with a background history of chronic alcohol abuse and longstanding, poorly controlled Type 2 DM. He initially received steroid therapy for the management of chronic lower extremity ulcers. This treatment was complicated by the development of generalized edema, including ascites. The patient now presents with persistent lower extremity ulcerations, and progressively worsening ascites. Clinical examination revealed the presence of ascites and stigmata of chronic liver disease, including spider nevi and the loss of axillary hair. He also complained of significant generalized weakness and fatigue. Diagnostic and therapeutic paracentesis revealed transudative ascites with a serum/ascites albumin gradient of 28 g/L. Cell count and culture of the ascites fluid did not reveal evidence of spontaneous bacterial peritonitis.

What is the differential diagnosis to explain these clinical findings?

Differential Diagnosis

Generalized Edema. Edema indicates expansion of the extracellular fluid compartment. This is caused by an imbalance between capillary and interstitial fluid hydrostatic and oncotic pressures. Gross, generalized edema is termed anasarca (Table 3). It can be characterized by periorbital puffiness, pitting edema of the extremities, trunk and face puffiness, pleural effusions, and ascites.[1,2] Edema can be categorized by its nature, extent, and location. Serial assessment of the amount of accumulated fluid can be done by daily measurements of the patient's abdominal girth or weight. One kg of weight gain equals 1 L of fluid accumulation.[3]

Table 3
Causes of Generalized Edema

- Congestive heart failure
- Nephrotic syndrome and other causes of kidney disease
- Nutritional disorders
- Cirrhotic liver disease

Edema due to congestive heart failure: Edema due to congestive heart failure can be caused by defective systolic emptying of the heart or impaired left ventricular relaxation. A reduction in the effective circulating volume triggers activation of the sympathetic nervous system and the renin-angiotensin-aldosterone (RAA) system leading to the retention of salt and water. The patient has a past history of an anterior myocardial infarction; however, he has not experienced dyspnea or paroxysmal nocturnal dyspnea. He does have orthopnea, but it was felt to be related to ascites and diaphragmatic embarrassment. JVP was normal, and the echocardiogram revealed only moderately impaired left ventricle (LV) function. These findings make cardiac causes of his edema less likely.

Edema due to nephrotic syndrome: This syndrome is characterized by proteinuria leading to a lower colloid oncotic pressure and net fluid movement into the interstitium. The decrease in effective circulating volume activates the RAA system, which promotes further salt and water retention. The patient did not have proteinuria within the nephrotic syndrome range (defined as urine protein > 3.5g/day), nor was there evidence of severe hypoalbuminemia (defined as serum albumin < 20 g/L). However, he did have mild hypoalbuminemia (31 g/L; normal albumin range is 35-50 g/L).

Nutritional edema: Nutritional edema is caused by a diet that is severely deficient in protein intake or following protein loss in the gastrointestinal tract. This promotes development of edema secondary to hypoalbuminemia. Examples include Beriberi heart disease or multiple peripheral arteriovenous fistulas. Starvation can promote edema through hypoalbuminemia, hypokalemia, and other caloric deficits.[1] The patient did not have any severe nutritional disorders.

Edema due to liver disease: Edema due to liver disease is multifactorial in nature. The patient had stigmata of chronic liver disease and a significant past history of alcohol consumption, suggesting liver disease as a possible cause for his ascites.

The serum ascites: albumin gradient of 28g/L indicates the presence of portal hypertension (serum ascites:albumin gradient = serum albumin - serum ascites; gradient >11g/L shows portal hypertension). Two hypotheses for the development of ascites in cirrhosis include the underfill theory and the overfill theory. In the underfill theory, portal hypertension and hypoalbuminemia lead to transudation of sodium and water into the peritoneum, causing a decrease in effective circulating volume. This results in subsequent salt and water retention by the kidneys. In the overfill theory, liver disease primarily leads to the renal retention of sodium and water which secondarily "overflows" into the peritoneal cavity. A combined theory postulates that liver disease results in peripheral vasodilatation, causing a reduction in effective circulating volume, central vasoconstriction of the afferent arteriole of the kidney, and secondary angiotensin II-mediated reabsorption of sodium in the proximal convoluted tubules.[2]

Edema due to metabolic causes. The patient's TSH was normal, ruling out myxedema (as seen in hypothyroidism) as a cause of his edema.

Cirrhosis. Cirrhosis is an irreversible process of chronic injury to the hepatic parenchyma. It is the end result of hepatocellular regeneration and fibrous scarring that constitute the major responses of the liver to a variety of longstanding or repetitive insults.[4, 5, 6] After cardiovascular disease and cancer, cirrhosis of the liver is the third leading cause of death in patients aged 45- to 65-years in the Western world.[7] Cirrhosis may be classified by its etiological causes or pathologic features into a variety of subtypes (Table 4).[2, 4]

Table 4
Subtypes of Cirrhosis

1. Alcoholic
2. Biliary
3. Cardiac
4. Metabolic (Hemochromatosis)
5. Inherited (Wilson's Disease)
6. Drug- related (α-methyl-Dopa)
7. Viral (Hepatitis B and C virus)
8. Cryptogenic (no identified cause)
9. Other

Cirrhosis results in three major sequelae: portal hypertension and its complications, hepatocellular failure, and/or the development of hepatocellular carcinoma. The cirrhotic patient may present with mild, compensated disease, or with severe end-stage complications. The clinical and laboratory features of cirrhosis are extensive (Table 5).

Table 5
Clinical and Laboratory Features of Cirrhosis

* Ascites
* Jaundice
* Splenomegaly
* Spider angiomata, palmar erythema,
Fetor hepaticus, Dupuytren's contracture, caput medusae
Generalized muscle wasting
Bruising
Hepatic encephalopathy
* Loss of axillary and pubic hair
Males: testicular atrophy, gynecomastia

** asterisk indicates features of cirrhosis identified in this patient*

Bleeding from esophageal varices is a severe complication of cirrhosis. Esophageal varices are the result of porto-systemic shunting due to portal hypertension in the cirrhotic liver. The presence of coagulopathy may also contribute to bleeding.

Complications of ascites. Complications of ascites include the hepatorenal syndrome and spontaneous bacterial peritonitis (SBP). Hepatorenal syndrome is defined as functional renal failure. The kidneys are histologically normal but there is a decline in the glomerular filtration rate with an increase in serum creatinine, marked reduction in urinary sodium excretion, and the development of oliguria. SBP refers to infection of the ascites fluid. Presentation of SBP may include fever and abdominal pain; however, some patients may experience no signs and symptoms other than a change in mentation. Laboratory evaluation of the ascites fluid did not reveal the presence of SBP in this patient.

Alcoholic liver disease. Three main forms of evolving liver injury due to alcohol abuse can be described: fatty infiltration, alcoholic hepatitis, and alcoholic cirrhosis. In the majority of patients with chronic alcoholism, the fatty liver is benign and damage is potentially 100% reversible following a period of abstinence. However, alcoholic liver cirrhosis, representing end-stage disease, will develop in 10 to 20% of patients who continue to drink.[8] Variable factors associated with the development of alcoholic liver disease include the amount and duration of alcohol intake, genetic and metabolic factors, and the patient's underlying nutritional status. Not all individuals who abuse alcohol develop significant liver damage, however, a linear correlation exists between the duration and dose of alcohol use, and the development of alcoholic liver disease. The most common cirrhosis subtype, alcoholic liver cirrhosis, is more likely if alcohol consumption is greater than 160 g/day.[5] Alcoholic cirrhosis is the most severe form of alcohol-related liver injury.[9]

Most prominent in this patient was the presence of gross, generalized edema and ascites. Of clinical importance, the patient did not exhibit any signs and symptoms characteristic of hepatic encephalopathy, which includes: the presence of asterixis, changes in behaviour, or alterations in the level of consciousness. Although the patient quit drinking 1.5 years ago, he admits to a 20-year history of drinking up to 1180 g/week of rum.

Clinical Diagnosis: Alcoholic liver disease

Pathological Discussion

An ultrasound-guided percutaneous liver biopsy was performed. A 1.2 cm core of white liver tissue was excised and embedded *in toto*. Light microscopy of the biopsy sample revealed extensive areas of regenerative micronodule formation with interspersed fibrous septa and large areas of extinction (Figure 1). These findings were consistent with the patient's clinical findings indicative of alcoholic liver disease. Using a modified version of the standard Laennec scoring system for chronic liver disease, a diagnosis of severe cirrhosis with no evidence of recent activity was made.

There are a number of factors that may influence the ease with which a diagnosis of cirrhosis can be made from a liver a biopsy. The amount and quality of the tissue samples, the size and positioning of contained nodules, the type of biopsy needle and associated procedures used (i.e. biopsy with laparoscopy,

circumferential biopsy will influence the ease of making the diagnosis by reviewing pathologists. A number of other criteria are useful in attaining a tentative diagnosis of cirrhosis:[10]

- liver consistency at biopsy
- ease of specimen fragmentation
- abnormal structural changes (reticulin)
- hepatocellular changes such as regenerative hyperplasia, pleomorphism, large cell or small-cell dysplasia, and excess copper-associated protein.

Examination of the biopsy sample demonstrated the two requisite features for the diagnosis of cirrhosis: diffuse parenchymal injury *and* widespread fibrosis. Histopathologically, parenchymal injury gives the appearance of structurally abnormal nodules of regenerating hepatocytes surrounded by interconnecting bands of fibrous tissue/scarring.[3, 4, 7, 11] At least one nodule must be completely surrounded by fibrous tissue to support the diagnosis of cirrhosis.[5,6] Cirrhotic livers can be micronodular (all or most nodules < 3 mm in diameter), macronodular (nodules > 3 mm), or mixed. Fibrosis results from an imbalance between collagen production and degradation. It is a common finding in end stage chronic liver diseases; however, fibrosis alone is not necessarily synonymous with cirrhosis.

Ultrasound may also be helpful for the diagnosis of cirrhosis, but only if ascites is concomitantly present. Increased echogenicity and dense, irregularly distributed reflective regions characterize areas of cirrhosis. Ultrasound examination of this patient's liver revealed a coarse, nodular liver, which was small in size. In addition, a large amount of ascitic fluid was present.

Alcoholic liver cirrhosis is most commonly associated with micronodule formation. Furthermore, disease progression may convert micronodule formation into a nonspecific macronodular pattern. This process of conversion takes more than 2 years to develop and represents regeneration following abstinence.[5, 7]

In order to distinguish alcoholic hepatitis from other causes of liver disease, certain characteristic features in the biopsy sample were closely examined. Morphological changes induced by alcoholic hepatitis include ballooning of liver cells and the presence of Mallory bodies, perivenular fibrosis and usually, but not always, hepatocellular steatosis. The biopsy specimen did not show evidence of hepatocyte ballooning or Mallory bodies, and less than 1% of all hepatocytes contained evidence of large droplet steatosis. Fatty change is usually a marker of recent alcohol consumption and can be used to determine the timeframe of disease activity. Absence of significant steatosis in this biopsy corroborates the patient's assertion that he has remained abstinent from alcohol over the past 1.5 years. There were few inflammatory cells (lymphocytes or neutrophils), bile ducts were seen in normal numbers, and there was no evidence of cholestasis. The iron stain was negative indicating that the patient does not have any of the inheritable iron-depositing disorders, such as hemochromatosis or thalassaemia, and he does not have cirrhosis with siderosis. In addition, there were no ground glass cells, thereby ruling out a diagnosis of hepatitis B virus infection.[9,10]

Pathological Diagnosis: Alcoholic liver cirrhosis

Prognosis of Alcoholic Liver Cirrhosis

Alcoholic liver cirrhosis has a less favourable outcome in the elderly and in women. Cirrhosis is generally believed to be an irreversible process. However, with abstinence, and appropriate, timely therapy, the destructive process may be delayed. A number of disease features have been characterized which are known to have considerable prognostic value in determining patient outcome (Table 6).

Table 6
Features Associated with Improved Prognosis in Cirrhosis

- Alcoholic cirrhosis etiology offers a more favourable prognosis than cryptogenic (unidentifed) cirrhosis
- Reversible precipitating factor
- Improvement within 1 month of hospital therapy
- Absence of jaundice
- Diuretic responsive, minimal ascites
- Large liver size
- Serum albumin > 25 g/L; absence of hyponatremia
- Absence of bruising and coagulopathy
- Absence of histological hepatic changes other than fatty infiltration

In general, abstinence from alcohol consumption increases survival in patients with both compensated and decompensated liver disease. Patients with alcoholic liver cirrhosis and ascites who continue to drink heavily have the worst prognosis.[12] Prognosis may also be related to age. In one study, one-year mortality among patients over 60 years of age was 50%, compared with a mortality of 7% in patients under the age of 60 years.[13] Other prognostic indicators include amount of alcohol consumed, ratio of serum transaminases (AST/ALT), serum bilirubin and creatinine levels, size of esophageal varices, and severity of portal hypertension.[14] Liver failure is the most common cause of death in patients with alcoholic liver cirrhosis (observed in 27-51% of cases). Other significant causes of mortality include gastrointestinal hemorrhage (9-47% of cases), renal failure (1-8% of cases), hepatoma formation (5-16% of cases), and infections (3-17% of cases).[14, 15, 16]

Treatment Options

Various treatment options are available for the management of patients with cirrhosis and ascites. These approaches include dietary modification, pharmacologic regimens, and surgical interventions.

Dietary sodium restriction: Restricting salt intake will help to reduce the edema. A reasonable goal is a 40 mmol/day sodium diet.

Spironolactone: Spironolactone antagonizes the actions of aldosterone and is an effective diuretic agent in the management of ascites. It is potassium-sparing, thus limiting the development of hypokalemia. Potassium depletion in cirrhotic patients can contribute to the development of hepatic encephalopathy.

Patients who fail to respond to a combination of sodium restriction and diuretic therapy are said to be diuretic-resistant.

In these cases, repeated large volume paracentesis is beneficial. In addition to cosmetic and comfort benefits, it also lowers intra-abdominal pressure, resulting in a reduction in portal pressures, increased cardiac output, and a reduction in activation of neurohumoral effector mechanisms. The need to administer albumin in conjunction with large volume paracentesis remains controversial.[17]

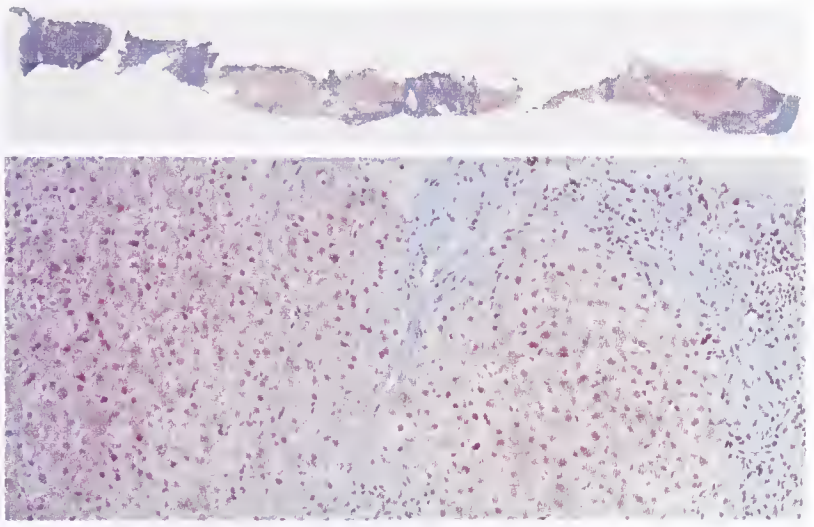

Figure 1.

Transjugular intrahepatic portosystemic shunt (TIPS): TIPS is a surgical procedure that lowers intrahepatic and portal venous pressures. It has primarily been used to control variceal bleeding but may also be used to manage patients with diuretic-resistant ascites. This radiologic intervention involves the creation of a tract within the liver parenchyma, which maintains patency between the portal and hepatic venous systems. Insertion of metallic stents redirect portal blood flow, thereby reducing portal venous hypertension and decompressing esophageal varices.[18] The maximum benefit of TIPS on renal function and urinary sodium excretion is often delayed for several weeks following the procedure. Patient mobility is higher in patients who undergo TIPS, but TIPS also includes risks which include the precipitation of hepatic encephalopathy, stent infection, and stent thrombosis. Complications of TIPS insertion include intraperitoneal hemorrhage, jugular venous thrombus formation, fever, bacteremia, renal failure, and hepatic encephalopathy.

Peritovenous shunts (PVS): PVS are surgically implanted subcutaneous catheter systems that divert ascites fluid from the peritoneal cavity to the venous system. Two available PVS systems are the Denver and Le Veen shunts.[18] The Le Veen Shunt involves the surgical insertion of a catheter incorporating a one-way pressure valve threaded under the skin to transfer fluid from the peritoneal cavity into the central circulation at the junction of the jugular vein or the superior vena cava.

Treatment of variceal bleeding: Beta-blockers have been demonstrated to reduce the risk of a first variceal bleed in patients with endoscopically visualized varices. Band ligation is the treatment of choice for the prevention of recurrent variceal bleeding.

Liver transplantation: In patients with decompensated end stage liver disease, orthotopic liver transplantation may be considered. Liver transplantation remains the only treatment that significantly improves the survival of patients with alcoholic liver disease who remain abstinent.[18]

Patient's Outcome

The diagnosis of severe alcoholic liver cirrhosis was discussed with the patient. Treatment included abstinence from alcohol and diuresis with furosemide and spironalactone. Although the patient has been abstinent from alcohol for 1.5 years and is committed to remaining abstinent, he did exhibit several features indicative of a poor prognosis: his ascites was minimally responsive to diuretic therapy; he had low serum albumin measurements and there was the presence of coagulopathy. There were also poor prognostic features on liver biopsy (multiple nodule formation and fibrosis, large areas of extinction, and distortion of the liver architecture).

On the day of discharge, an additional 2.0 L of ascitic fluid was removed. The discharge medications included Novolin 30/70 (30 units sc qam, 26 units sc qhs), furosemide 120 mg po daily, spironolactone 100 mg po daily, silver sulfadiazine topical ointment, and compression wrap of the lower extremity ulcers.

This patient is at increased risk for esophageal varices due to his existing portal hypertension. It was strongly recommended that he undergo a diagnostic esophago-gastro-duodenoscopy to determine whether varices were present. ß-adrenergic blockade for the prevention of variceal bleeds may be considered. In addition, the possibility of TIPS insertion if the ascites did not respond to therapy was discussed with the patient.

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Surgery Rounds

Patrick S. Tawadros, B.Sc. (0T2) and Aric Storck, B.Soc.Sc. (0T2)

Case 1

Tirone E. David, M.D., F.R.C.S.(C), F.A.C.S., and
Ehud Raanani, M.D.
Division of Cardiovascular Surgery, Toronto General Hospital

Five years ago, an 80 year old man underwent mitral valve repair for mitral regurgitation. Recently, he presented with increasing shortness of breath and cardiac arrhythmias. An echocardiogram revealed recurrent moderate mitral regurgitation. He was treated with the antiarrhythmic amiodarone, readmitted for redo mitral valve repair, and fitted with a pacemaker. Despite these interventions, he experienced persistent shortness of breath post-operatively.

What is the diagnosis?

FIGURE 1.1. *Chest x-ray*

FIGURE 1.2. *CT scan of the thorax.*

Case 2

Richard D. Weisel, M.D., F.R.C.S.(C)
Division of Cardiovascular Surgery, Toronto General Hospital

A 60 year old man presented to the emergency department with a 2 hour history of persistent retrosternal pain. Ten years ago, he suffered a myocardial infarction and has had progressive angina over the last two months with prolonged episodes of rest angina. He was found to have suffered a non-Q wave myocardial infarction with an elevated CK-MB level. While in hospital, he continued to have chest pain despite full medical treatment. His cardiac risk factors included smoking, hyperlipidemia, and hypertension. Upon admission, cardiac catheterization was performed revealing the following angiograms.

What is the diagnosis?

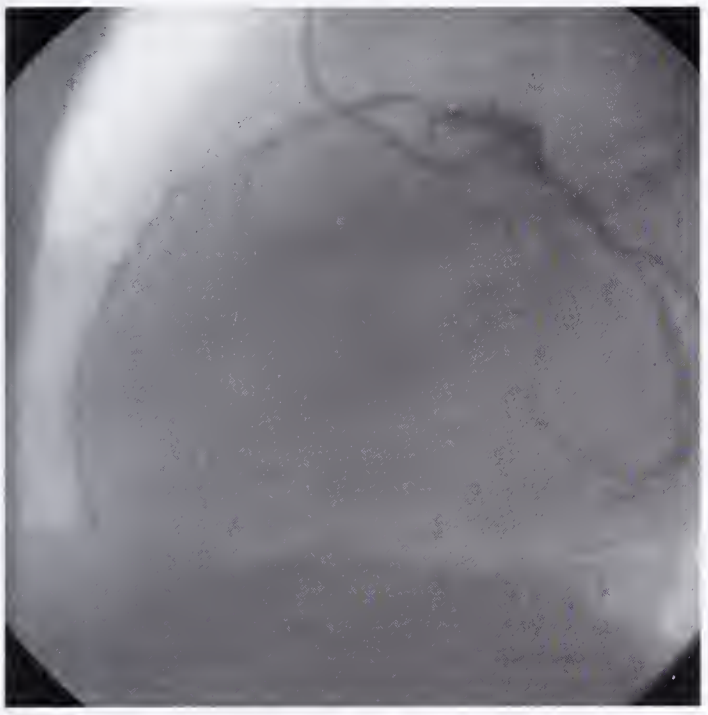

FIGURE 2.1. *Angiogram of left coronary artery.*

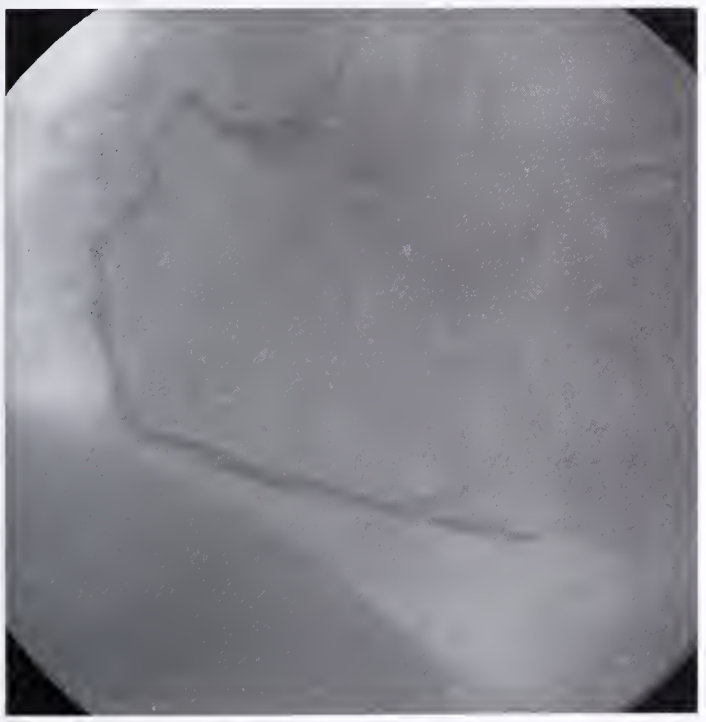

FIGURE 2.2. *Angiogram of right coronary artery.*

Case 3

Ori D. Rotstein, M.D., F.R.C.S.(C), F.A.C.S., and
Richard D. Bloomberg, M.D.
Division of General Surgery, Toronto General Hospital

A 58 year old woman presented with an acute onset of fever and chills, abdominal pain, reduced appetite, and mild jaundice. The following CT scans were obtained.

From Figure 3.1, can you determine the diagnosis?

Do you notice anything else of significance in Figure 3.2?

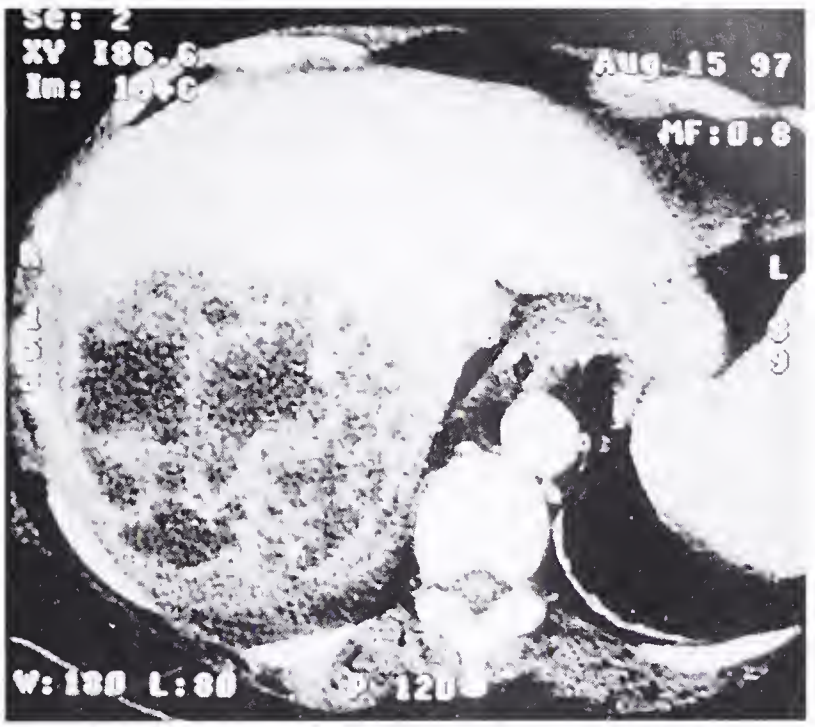

FIGURE 3.1. *CT scan of the abdomen.*

FIGURE 3.2. *CT scan of the abdomen showing a cut inferior to Figure 3.1.*

Case 4

Bruce Taylor, M.D., F.R.C.S.(C), F.A.C.S.
Division of General Surgery, Toronto General Hospital

A 28 year old woman was well until she came to the emergency department with severe left upper quadrant abdominal pain. Blood work revealed an elevated serum amylase level. On physical examination she was found to have a firm, palpable mass in her upper abdomen. The following CT scans were obtained.

What is the diagnosis?

FIGURE 4.1. *CT scan of the abdomen with i.v. and p.o. contrast.*

FIGURE 4.2. *CT scan of the abdomen showing a cut 6 cm inferior to Figure 4.1.*

Case 5

Mark Bernstein, B.Sc., M.D., F.R.C.S.(C)
Division of Neurosurgery, Toronto Western Hospital

A previously healthy 37 year old man presented with a 10 day history of rapidly progressing headache and right-sided numbness and weakness. Eventually, he developed horizontal ophthalmoplegia, right-sided hemiplegia, left fifth and seventh cranial nerve palsies, an absent gag response, and ultimately became comatose. The following MRI studies were obtained.

What is the diagnosis?

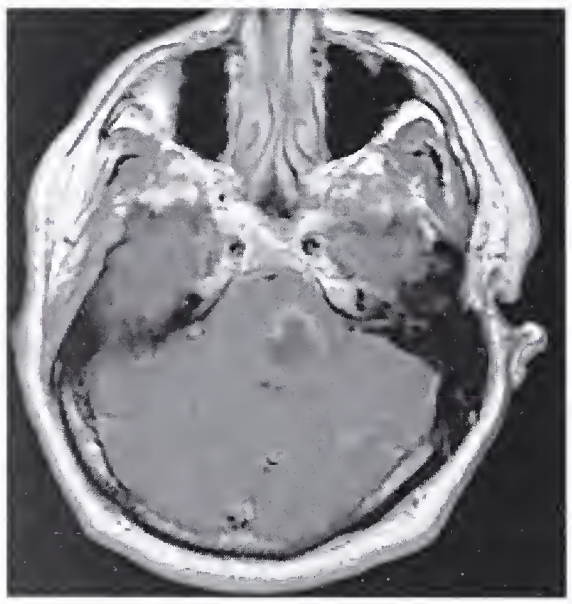

FIGURE 5.1. *Axial T1 MRI of the brain with gadolinium enhancement.*

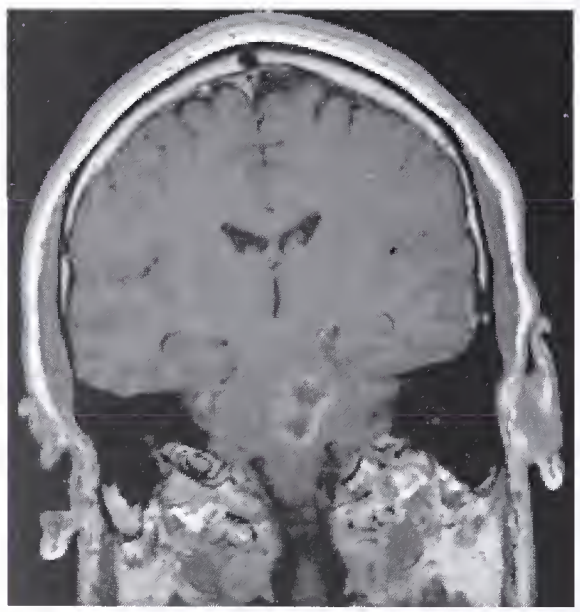

FIGURE 5.2. *Coronal T1 MRI of the brain with gadolinium enhancement.*

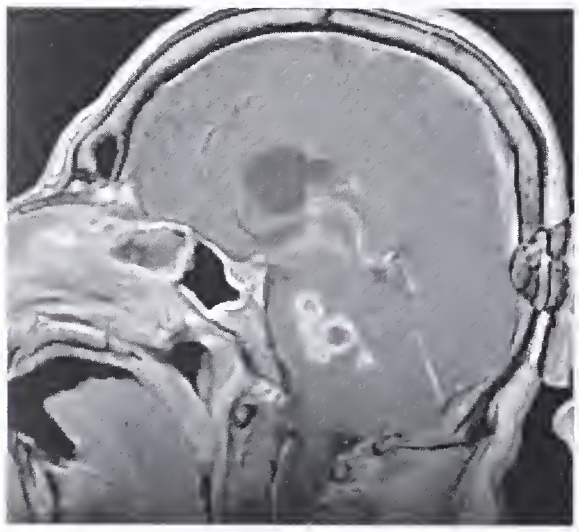

FIGURE 5.3. *Sagittal T1 MRI of the brain with gadolinium enhancement.*

Case 6

Peter B. Dirks, M.D., Ph.D., F.R.C.S.(C)
Division of Neurosurgery, Hospital for Sick Children

A 2 1/2 year old baby girl presented with a 2 month history of vomiting and a recent 1 week history of progressive irritability with increasing lethargy, drowsiness and gait ataxia. She was afebrile. The following MRI studies were obtained.

What is the diagnosis?

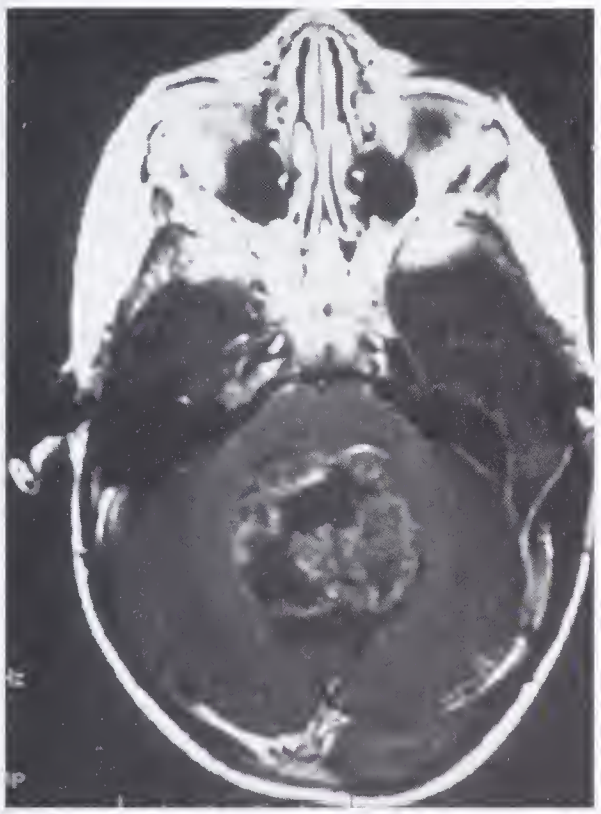

FIGURE 6.1. *Axial T1 MRI of the brain with gadolinium enhancement.*

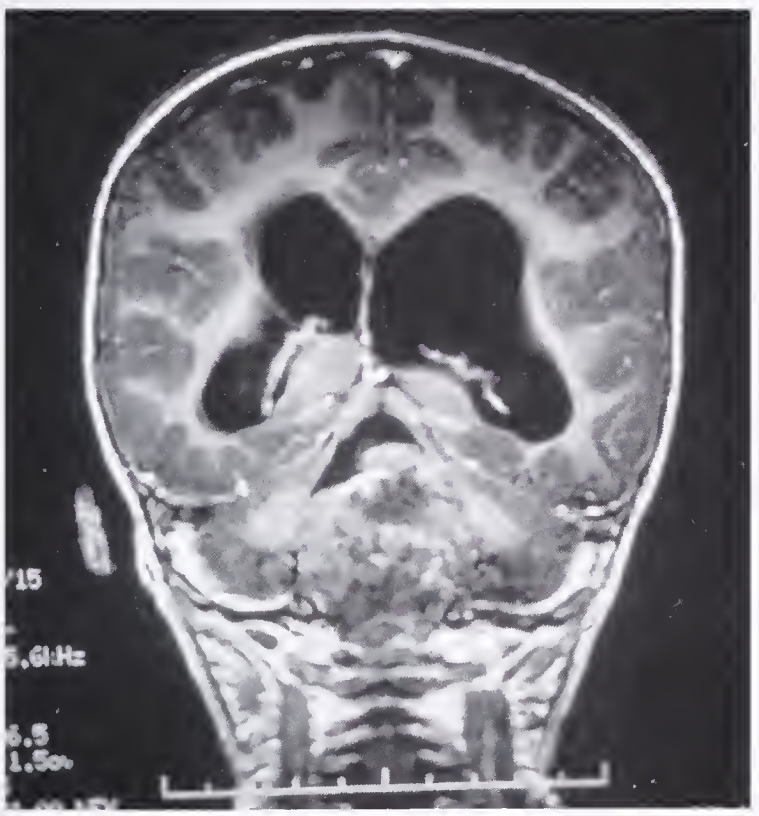

FIGURE 6.2. *Coronal T1 MRI of the brain with gadolinium enhancement.*

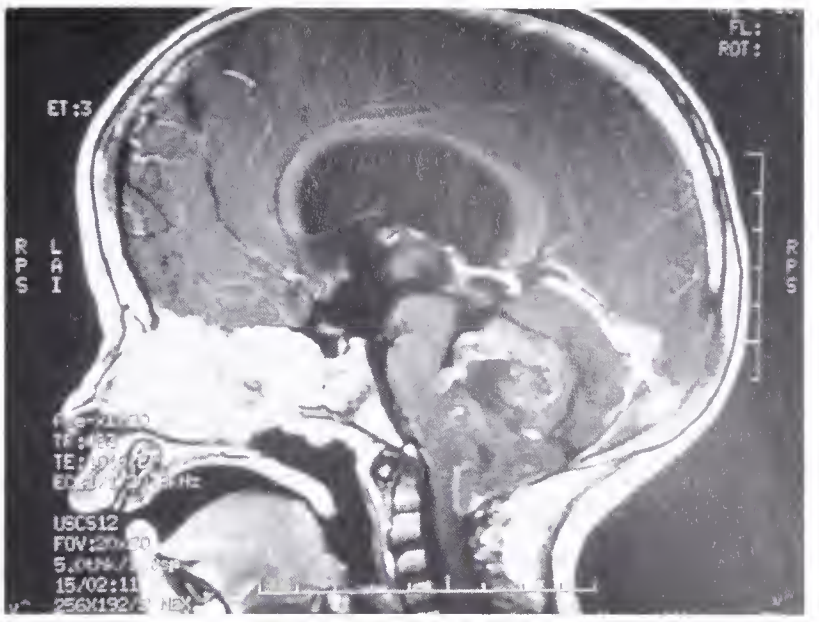

FIGURE 6.3. *Sagittal T1 MRI of the brain with gadolinium enhancement.*

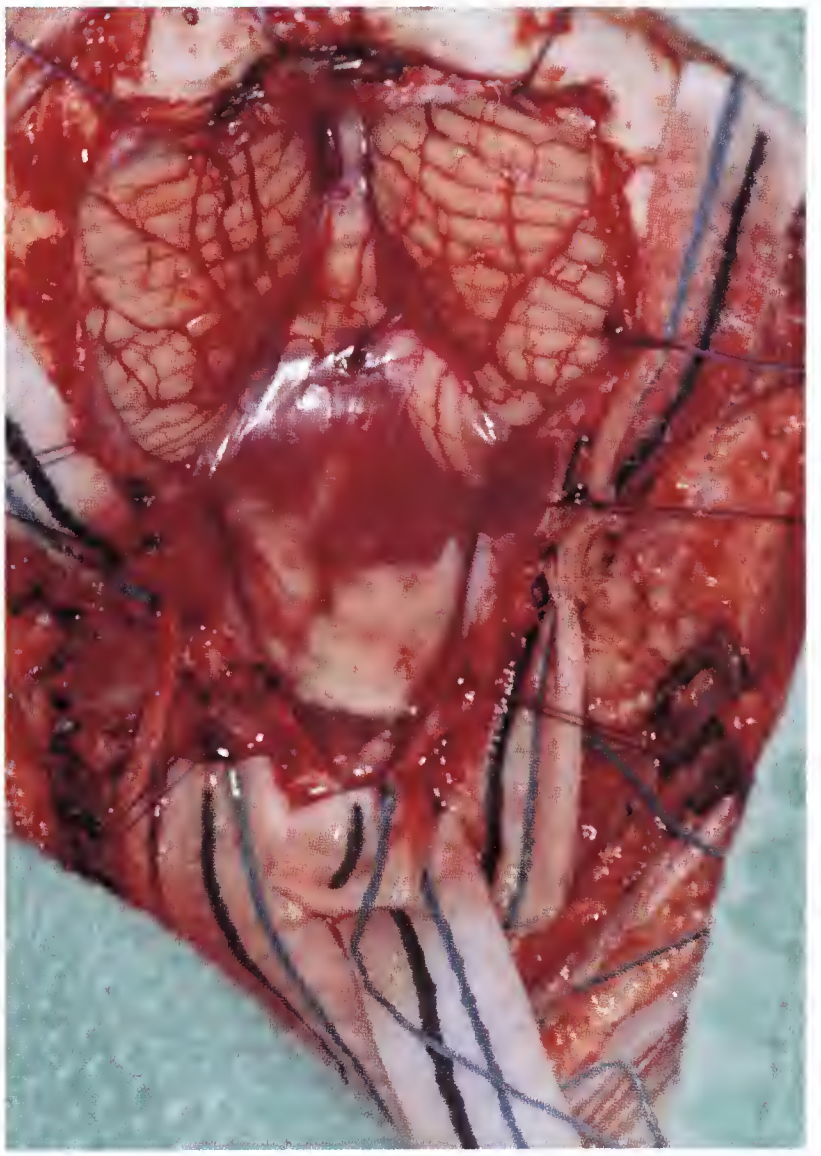

FIGURE 6.4. *Intra-operative photograph.*

Case 7

Charles H. Tator, M.D., Ph.D., F.R.C.S.(C)
Division of Neurosurgery, Toronto Western Hospital

A 16 year old girl presented with decreased hearing in her left ear, diminished balance, some facial numbness and difficulty focusing her vision. On physical examination, she was found to have nystagmus on right and left lateral gaze and on upward gaze. There was a rotatory component to her nystagmus. She also had diminished sensation on the left side of her face and a diminished left corneal reflex. There was no apparent facial paresis and her gait was normal. She was known to have neurofibromatosis type II. The following MRI studies were obtained.

What is the diagnosis?

FIGURE 7.1. *Axial T1 MRI of the brain with gadolinium enhancement.*

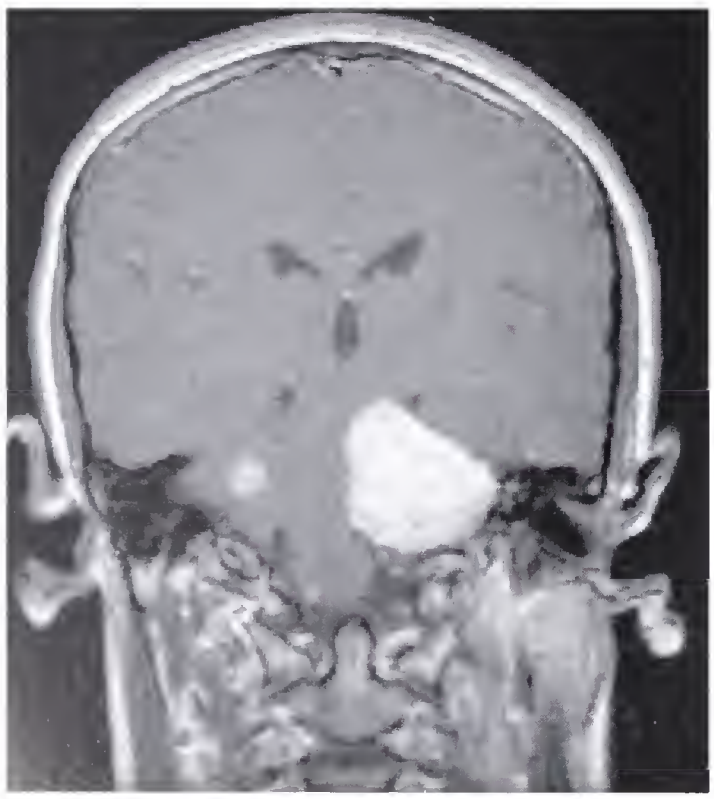

FIGURE 7.2. *Coronal T1 MRI of the brain with gadolinium enhancement.*

Case 8

Mark Mandelcorn, B.Sc., M.D., C.M., F.R.C.S.(C)
Division of Ophthalmology, Toronto Western Hospital

A 42 year old woman noticed a faint arc of light moving around the periphery of her right visual field every few seconds while in the dark. The following morning, she noticed floaters in the same visual field and decided to consult her family physician. Using a direct ophthalmoscope, her physician noticed small blood clots in her vitreous cavity and immediately referred her to an ophthalmologist. That night the patient noticed that the lower field of vision in her right eye was becoming progressively blocked as if a curtain was rising from below. The following day the ophthalmologist re-examined the retina using an indirect ophthalmoscope (Figure 8.1).

What is the diagnosis?

FIGURE 8.1. *Photograph of retina.*

Case 9

Allan E. Gross, M.D., F.R.C.S.(C)
Division of Orthopaedic Surgery, Mount Sinai Hospital

A 46 year old woman presented with a 2 year history of moderate to severe pain in her right hip that was initiated by a heavy fall on her right side. Physical examination revealed a significantly decreased range of motion of her right hip in all planes. She had a markedly antalgic gait, but no apparent leg shortening. The following images were obtained.

What is the diagnosis?

FIGURE 9.1. *Pelvic x-ray from 2 years ago.*

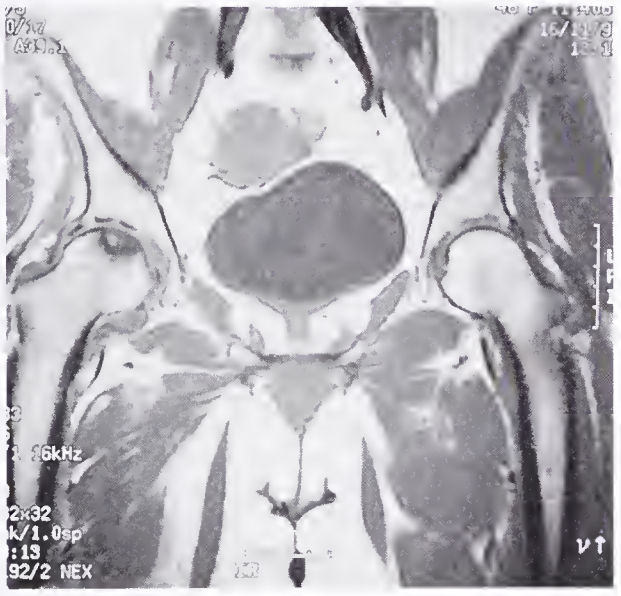

FIGURE 9.2. *Pelvic MRI from 1 year ago.*

FIGURE 9.3. *Recent pelvic x-ray.*

Case 10

John Rutka, M.D., F.R.C.S.(C)
Division of Otolaryngology, Toronto General Hospital

A 45 year old man had a history of incomplete hearing loss in his left ear accompanied by a chronic, painless, foul-smelling discharge. He presented to his family physician after two days of severe dizziness and complete loss of hearing in the left ear. His other complaints included ataxia, nausea, and vomiting. On physical examination he was found to be vertiginous with right beating nystagmus in all directions of gaze. Using an otoscope, the physician observed a perforated tympanic membrane and a lesion in the attic region (Figure 10.1). The Rinne test was positive in the right ear and negative in the left. The Weber test lateralized to the right ear. The patient was immediately rushed to the emergency department where a CT scan was performed (Figure 10.2).

What is the diagnosis?

FIGURE 10.1. *Photograph of external auditory meatus and tympanic membrane.*

FIGURE 10.2. *Coronal CT scan of the ear.*

Diagnoses

Case 1

Dx. Amiodarone Induced Pulmonary Fibrosis

This man's initial presentation of increasing shortness of breath was probably due to his recurrent moderate mitral regurgitation. However, the persistent post-operative shortness of breath was caused by a complication of the antiarrhythmic drug Amiodarone that caused the pulmonary fibrosis evident on the films.

Case 2

Dx: Coronary Artery Disease with Unstable Angina

This patient's angiograms reveal significant coronary artery disease. Several lesions can be seen causing stenoses in the left anterior descending artery (the vessel on the left side of Figure 2.1), the circumflex artery (the vessel on the right side of Figure 2.1), and the right coronary artery (Figure 2.2). This combination of lesions is commonly referred to as triple vessel disease. Because of his symptoms and his extensive coronary disease, this patient was referred for urgent coronary revascularization. Although the risks of surgery in this case are increased (operative mortality of ~5%), the risks of continued medical therapy are even higher (~25% mortality). The patient's operation went well. He recovered quickly from quintuple aorto-coronary bypass surgery and subsequently became free of anginal symptoms.

Case 3

Dx: Multiloculated Liver Abscess

Figure 3.1 reveals a rather large multiloculated liver abscess that was percutaneously drained and treated with antibiotics. A follow-up CT scan showed significant reduction in the size of the abscess. Incidentally, the initial CT scan also reveals an area of irregular bowel wall thickening involving the cecum and right proximal colon (Figure 3.2). Further investigations confirmed the presence of a well-differentiated adenocarcinoma of the right colon requiring resection.

Case 4

Dx: Cystic Tumour of the Pancreas

The initial radiological diagnosis of a persistent pancreatic pseudocyst led to surgery, which confirmed the presence of a huge cystic mass arising from the anterior head, body and proximal tail of the pancreas. The lesion was felt by the surgeon to be unresectable other than by total pancreatectomy. The cyst was therefore opened, its contents aspirated and drained internally using a Roux-y cyst-enterostomy. Initial quick sections of the cyst wall indicated benign tissue consistent with pseudocyst, but subsequent postoperative histopathological analysis revealed epithelial neoplasm of the pancreas of papillary nature. Upon referral, a group of radiologists and surgeons with a special interest in pancreatic diseases reviewed the initial CT scans and confirmed the diagnosis of cystic tumour of the pancreas. Repeat laparotomy was planned to resect the tumour and reconstruct the intestine previously used for internal drainage.

Case 5

Dx: Brainstem (Pontine) Abscess

This patient's MRI studies reveal a ring-enhancing lesion deep in the brainstem. The differential diagnosis included a hematoma, a tumour such as glioma or metastasis, or an abscess. The prospect of a vascular lesion was ruled out by initially ordering an angiogram, which was negative. It was then decided to perform a stereotactic biopsy of the left brainstem lesion. This procedure confirmed the relatively rare diagnosis of brainstem abscess. Treatment included stereotactic aspiration and appropriate antibiotic treatment. Eventually, the patient improved neurologically and returned to normal mental status. He retained some hemiparesis and hemihypesthesia with a sixth nerve paresis, but is expected to improve with time.

Case 6

Dx: Anaplastic Ependymoma

This patient's MRI studies reveal a large 4th ventricular mass lesion measuring roughly 4-5cm in diameter. The mass extended out through the foramen of Magendie and spread along the dorsal medulla and through the foramen magnum along the dorsal cervical cord. Surgical resection was performed and the diagnosis of anaplastic ependymoma was confirmed by pathology. The tumour was invading the floor of the 4th ventricle and medulla, and could not be completely resected. Ependymomas are the third

most common posterior fossa tumour in children after cerebellar astrocytomas and medulloblastomas. These tumours arise within the 4th ventricle and can spread through the foramen of Magendie (to the dorsal medulla and cervical cord as in this case) or through the foramen of Lushka (into the cerebellopontine angle). This case illustrates typical clinical and imaging features of 4th ventricular ependymomas. A clinical clue to the pathological diagnosis is the history of vomiting, which precedes other symptoms of raised intracranial pressure (such as headache and decreased level of consciousness). The reason for this particular chronology in ependymoma is that the tumour most often arises from the floor of the 4th ventricle and thereby disturbs the area postrema. "Irritation" of this emetic chemoreceptor zone triggers vomiting early in the course of the disease.

Case 7

Dx: Bilateral Vestibular Schwannomas

This patient's MRI studies reveal bilateral vestibular schwannomas (acoustic neuromas), which are characteristic of patients with neurofibromatosis type II. The left tumour (over 4 cm in diameter) has grown across the midline causing marked compression of the pons and medulla. Vestibular schwannomas are relatively rare, benign tumours that grow from the vestibular portion of the eighth cranial nerve. This patient underwent an 80% surgical resection of the left tumour after stereotactic radiosurgery failed to slow its growth. She made an excellent recovery from the microsurgery and will require further radiation treatment.

Case 8

Dx: Spontaneous Rhegmatogenous Retinal Detachment

This woman suffered a detached retina caused by a retinal tear. The flashes of light signified traction on the retina that caused the retinal tear (Figure 8.1). The floaters signified bleeding from torn retinal blood vessels in the area of the retinal tear. An emergency scleral buckling procedure was performed to indent the sclera to meet the detached retina and allow it to reattach. The patient was discharged two hours after surgery and had normal vision the next day.

Case 9

Dx: Avascular Necrosis of Femoral Head

This patient had a series of periodic pelvic x-rays since the time of her fall 2 years ago. Although the initial x-ray does not show any evidence of necrosis (Figure 9.1), the diagnosis could already be made from her MRI of 1 year ago that revealed an area of darkness in the femoral head indicative of necrosis (Figure 9.2). Her recent x-ray, which revealed complete loss of joint space and underlying bone collapse due to osteonecrosis (Figure 9.3), reaffirmed the diagnosis. She was advised to undergo a total right hip replacement.

Case 10

Dx: Cholesteatoma with Suppurative Labyrinthitis

This man had a cholesteatoma with erosion through the otic capsule into the lateral semicircular canal with accompanying suppurative labyrinthitis. A mastoidectomy was performed to exteriorize the disease and prevent it from growing into the brain and causing further damage. Surgery at this point was only for damage control: the loss of hearing and vestibular function is permanent. All patients with chronic discharging ears should be referred to an otolaryngologist to avoid such complications.

Ultrasound Biomicroscopy: A Promising Candidate for Monitoring Tumour Response to Therapy in Cancer Patients

Christopher Tam, B.A. (OT2) and Lana Tan, B.Sc. (OT2)

(a) Untreated control pellet

(b) 24 hours after treatment with cisplatin, a drug commonly used in chemotherapy that causes apoptosis.

FIGURE 1. *Ultrasonic images of AML-5 cell pellets (4 mm in each panel). The changes in ultrasonic speckle intensity are associated with the cell of apoptosis.*

In patients with cancer, tumour responses to therapy are typically measured three to four weeks into the course of treatment. A combination of inspection, palpation, biopsy, and radiographic imaging of the tumour is currently used to determine whether treatment has been successful. However, these methods have shortcomings; an ideal procedure would be non invasive, accurate, and one that could be performed shortly after the initiation of therapy. These criteria may soon be met with the introduction of high frequency ultrasound biomicroscopy (UBM) in the clinical setting.

UBM was first developed by Dr. Michael Sherar in the late 1980's at the Ontario Cancer Institute/Princess Margaret Hospital in Toronto with then Ph.D. supervisor Dr. Stuart Foster. Its imaging potential was demonstrated in the differentiation of necrotic and viable cells in tumour spheroids.[1] Since then, the applications of UBM have expanded rapidly to include the diagnosis and assessment of ocular disease,[2] currently performed at many centers including the Eye Clinic at Princess Margaret Hospital, and of psoriasis.[3] It has also been used to study embryonic brain development in mice.[4]

The idea of employing UBM in cancer care centers is a recent one, and is being investigated by a team of researchers at Princess Margaret Hospital including Drs. Gregory Czarnota, Michael Kolios, Michael Sherar, and John Hunt. Current cancer treatment, including radiation therapy and chemotherapy, works by inducing apoptosis in tumour cells, a process to which UBM is exquisitely sensitive. Nuclear condensation and fragmentation, changes that characterize apoptosis, lead to a six-fold increase in the amount of ultrasound backscatter.[5] Consequently, areas of tissue with apoptotic cells appear very bright in a conventional ultrasound B-scan image as compared to viable cells (Figure 1). Preliminary data from studies involving patients with superficial lymphoma and melanoma demonstrate a large increase in ultrasound scattering after the onset of therapy as compared to pre-treatment.

As a clinical tool to assess tumour response to therapy, UBM provides several advantages over current practices. The non-invasive nature of the procedure results in minimal discomfort to the patient and, hence, allows for more frequent monitoring. Moreover, UBM provides a means of detecting apoptosis over the entire volume of tumour and surrounding tissues. Most importantly, the expediency at which apoptosis can be detected by UBM allows for the timely detection of resistant tumours and for timely treatment modifications.

However, the very fine resolution and high contrast enjoyed by UBM comes at a price: lack of penetration depth. Imaging with ultrasound in the 40-100 MHz range is limited to a depth of approximately 3-5 mm, depending on the tissue type. Consequently, UBM has been restricted to imaging superficial tissues, such as the skin and the anterior chamber of the eye. This may soon be overcome with the development of needle and catheter-based UBM systems for imaging deeper tissues and blood vessels *in situ*.

Many questions surrounding the use of UBM still persist and require active investigation. Nevertheless, the foundations have been laid and the outlook is promising. In time, UBM may become part of a standard and comprehensive treatment plan for patients with cancer.

Acknowledgments

The authors would like to thank Drs. Gregory Czarnota, Michael Kolios, and Michael Sherar for their helpful comments during the preparation of this article.

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Internal Medicine

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Endocrinology: Key Questions Answered. By John Laycock and Peter Wise. Oxford University Press, 1997, 323 pages. Reviewed by Chris McIntosh, M.Sc. (0T1), Vol. 75, No. 2, March 1998

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Respiratory Physiology: People and Ideas. Edited by John B. West. Oxford University Press, 1996, $121.95. Reviewed by Deep Chatha, M.Sc. (9T9), Vol. 74, No. 2, March 1997

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Neurology

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Oncology

Cancer Biology, 3rd ed. By Raymond W. Rudden. Oxford University Press, 1995, 520 pages. $68.95. Reviewed by Ally-Khan Somani, B.Sc.H. (M.D./Ph.D. program, year 3), Vol. 73, No. 3, May 1996

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Paediatrics

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Patient Information

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The Complete Breast Book. By June Engel, Ph.D. Key Porter Books, 1996, 288 pages, $21.95. Reviewed by Melinda Anne Musgrave, Ph.D. (9T8), Vol. 73, No. 2, March 1996

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Psychiatry

Counseling for Sexual Abuse: A Therapist's Guide to Working with Adults, Children and their Families. By Kathy MacDonald, Ian Lambie and Les Simmons. Oxford University Press, 1995. Reviewed by Michele Farrugia, M.Sc. (9T8), Vol. 73, No. 3, May 1996

The Massachusetts General Hospital Guide to Psychiatry in Primary Care. Edited by Theodore A. Stern, John B. Herman and Peter L. Slavin. McGraw-Hill, 1998, 696 pages. Reviewed by Todd P.W. McMullen (0T2), Vol. 76, No. 3, May 1999

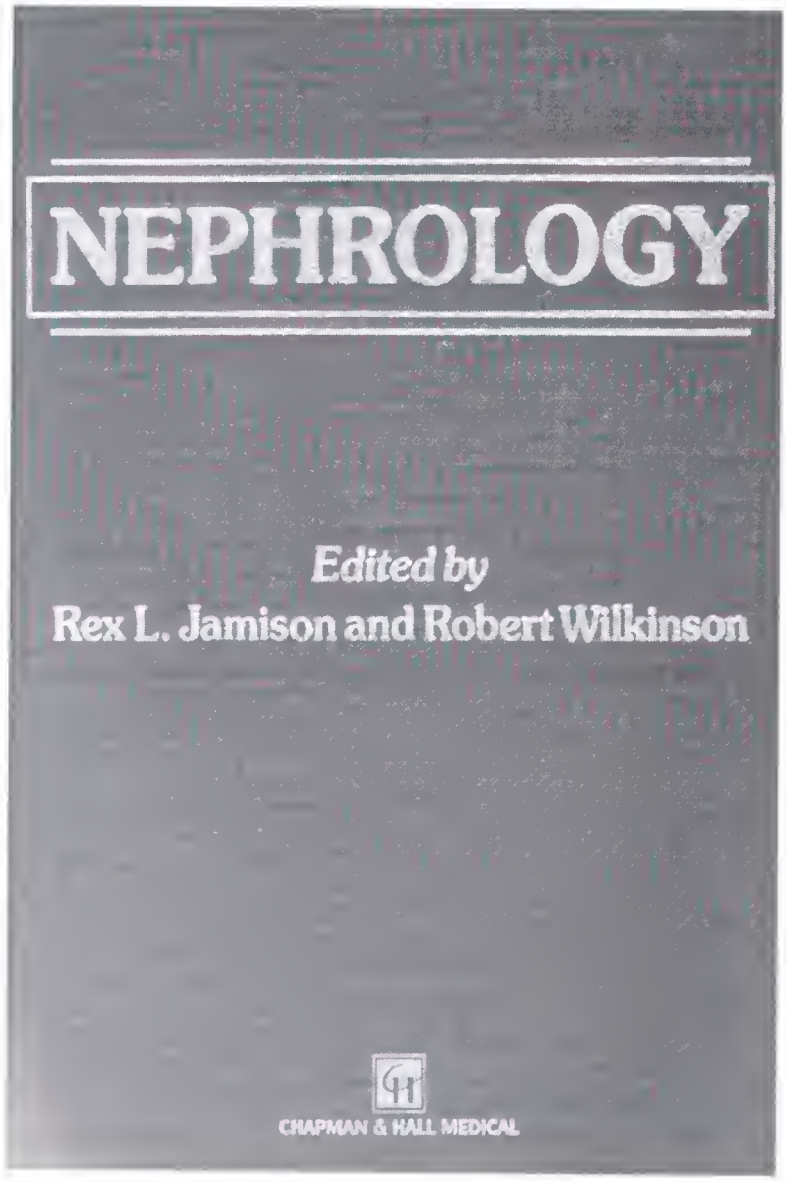
UTMJ Reviews – Internal Medicine

Nephrology

Reviewed by Dan Perri, B.Sc Phm. (0T0)

Editors: Rex L. Jamison and Robert Wilkinson
Publisher: Chapman & Hall Medical
Date of Publication: 1997
Number of Pages: 1152
Cost: Hardcover edition $360 (CDN).

Strengths:	Brief chapters, excellent tables, beautiful diagrams and photographs
Weaknesses:	Expensive, somewhat dated material, inconsistent referencing
Audience:	Internal medicine and nephrology residents, fellows, and practising physicians



Nephrology is a relatively new term, dating back to the 1960s. Prior to that time, several pocketbooks on renal physiology and body fluids were available, but textbooks on nephrology did not exist. Over the years, nephrology textbooks have grown larger with some standard texts having evolved into multiple-volume editions ranging from 2000 to 4000 pages. Jamison and Wilkinson comment in their preface that they set out to write *Nephrology* with three clear objectives: to produce a book that can easily be carried between the office and clinic with a balanced content between encyclopaedic renal texts and pocket manuals; to provide an international perspective about issues in nephrology; and assure a readable text by judicious selection of authors and "careful – even aggressive – editing".

The result of their work, *Nephrology*, is 1152 pages and weighs seven pounds – hardly easy to carry to and from work. The contributors include 114 distinguished physicians: 62 from the United Kingdom, 39 from the United States, 2 from Canada (Kevin Burns and David Levine from the University of Ottawa), 10 from a handful of Western European countries, and 1 from New Zealand. While this list of contributors would qualify it as an "international" list of contributors, I do not believe that it can represent a truly global perspective as all authors have fac-

ulty appointments in Western countries. Where the editors do shine, however, is in their ability to have "aggressively edited" the text down to 1152 pages. Despite its "small" size, *Nephrology* is quite inclusive. There are 89 chapters divided into 3 major sections that deal with normal structure and function of the kidney, impaired renal function, and diseases of the kidney and their treatment.

The contents of this book are similar to other renal texts and include anatomy, physiology, body fluid regulation, blood pressure, renal impairment, fluid and electrolyte disorders, inherited and developmental renal disease, disorders secondary to renal dysfunction, pregnancy related kidney disease, renal involvement in systemic illnesses, medical management of renal disease, dialysis, and renal transplantation. Surprisingly, there are chapters devoted to dermatologic ramifications of kidney disease, growth factors in kidney development and disease, the aging kidney, arachidonic acid metabolism, nutrition in renal disease, and a good synopsis of renal diagnostic imaging. However, discussions on calciphylaxis, cholesterol emboli, non-renal acid-base disorders, and drug-induced renal disorders (such as lithium, cocaine, milk-alkali syndrome, or radiocontrast nephropathy) could not be found. The text is also somewhat dated – for example renal tubular acidosis is referred to in the old "proximal" or "distal" classification rather than RTA type number. As well, diabetics are referred to as "insulin dependent" or "non-insulin dependent" as opposed to type 1 or type 2. Despite having been only recently marketed, the text has a 1997 copyright date.

The greatest strength of *Nephrology* is its use of helpful tables, algorithms, graphs, diagrams, and photographs. These are generally easy to understand and complement the text nicely. The colour photographs of renal biopsy specimens and physical exam findings are stunning. Histology slides and electron micrographs are large and clear. The overall layout and design is visually appealing. There are, however, some inconsistencies with writing style, especially referencing, as some chapters provide clearly numbered references within the text while others provide only a reading list at the end of the chapter.

The text focuses on clinically relevant issues but also provides useful background information for less experienced clinicians and those who have forgotten the intricacies of renal physiology learned in medical school. While medical personnel can use it at various stages of training, the material is targeted at practising residents and staff physicians on a nephrology service. This book can serve as a quick and easy reference for rounds or act as the starting point for a literature search, although many references are now quite dated. Unfortunately, at $360, it is a text not affordable by most medical students, interns, or new residents. Nonetheless, when compared to its multi-volume set competitors, *Nephrology* is much more user-friendly and for this reason alone is likely to be used on a regular basis rather than collect dust on a bookshelf.

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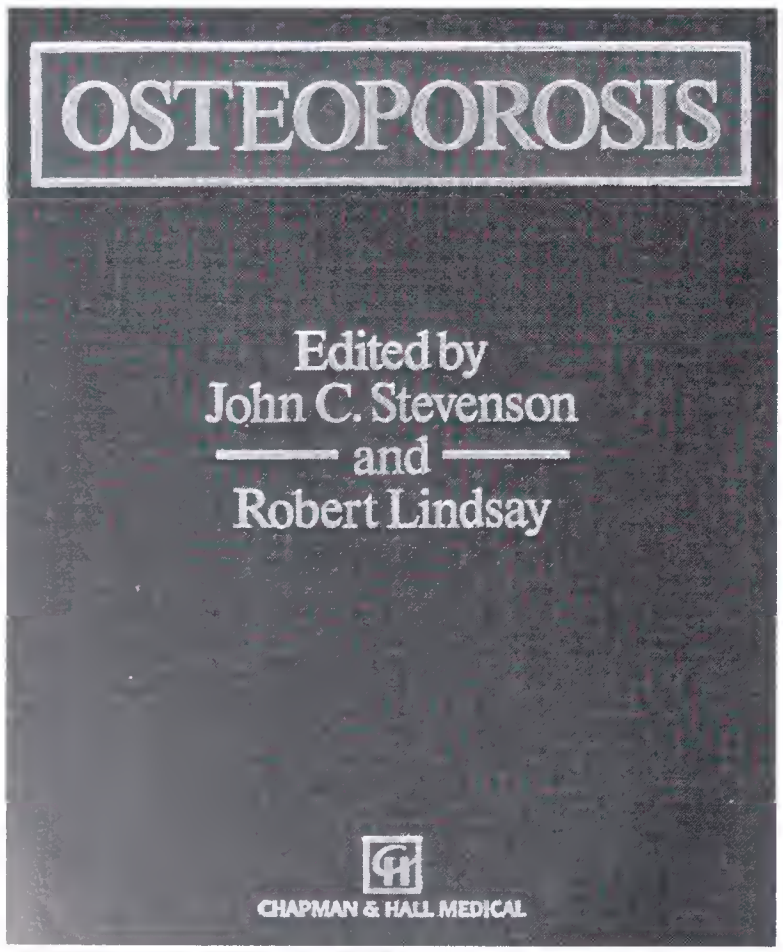
UTMJ Reviews – Internal Medicine

Osteoporosis

Reviewed by Grant Chen, B Sc. (OTO)

Editors: John C. Stevenson and Robert Lindsay
Publisher: Chapman & Hall Medical
Date of Publication: 1998
Number of pages: 380 pages
Cost: Hardcover edition, $157.95 (CDN)

Strengths:	An exhaustive discussion and review, with references, of all aspects of osteoporosis, from basic scientific principles to clinical aspects; excellent chapters on bone histomorphology and studies in therapeutic options
Weaknesses:	The topics are presented in a disorganized fashion and the highly-specialized nature of the content leads to segments that are irrelevant to a majority of practisng clinicians
Audience:	Graduate students doing research in metabolic bone disease, practising physicians specializing in osteoporosis



"The real voyage of discovery consists not in seeking new lands, but in seeing with new eyes." Marcel Proust, the French novelist, must have known something about the study of disease. Osteoporosis has been a well-known disease entity for many years and is commonly encountered in clinical practice, but we are continually learning new information using, as Monsieur Proust suggests, new 'eyes' or techniques. *Osteoporosis*, edited by John C. Stevenson and Robert Lindsay, is an in-depth look into the disease which the World Health Organization defines as "a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to increased bone fragility and a consequent increase in fracture risk."[1] To accomplish this daunting task, the book is a product of contributions from international experts (mostly from the United States and United Kingdom) in the field of metabolic bone disease. With the demographics of the population shifting towards older age groups, the number of new cases of osteoporosis will only increase. The morbidity and mortality from injuries related to osteoporosis

are also extremely high and, as such, it is a clinically significant entity that warrants further probing.

Osteoporosis is organized into 19 chapters. The book begins with the basics of bone structure and the pathogenesis and epidemiology of osteoporosis. This is followed by a discussion of bone measurement and then a series of chapters dealing with various therapeutic studies and approaches to osteoporosis such as physical activity, estrogen, and bisphosphonates. The book finishes with aspects of rehabilitation, orthopedic intervention, and a look at future strategies for the study of osteoporosis. The order of topics presented in the book leaves the reader jumping back and forth between chapters. The text starts with the basic science of bone structure and then jumps to a clinical correlate, namely osteoporosis and its epidemiology, then returns to the basic science of bone structure and methods of measuring it. The book would be better suited if it finished reviewing all of the basic science, starting with bone structure and the basics of bone measurement, before going on to its clinical applications.

Each chapter is clearly written and easy to understand, however there are points within the basic science portion of the book that are quite esoteric. The latter chapters on the relationships between osteoporosis and treatment strategies are the most relevant to clinicians. There are a number of references which allow the reader to examine particular studies and sources more closely. However, stylistically, the way in which the references are placed within the text disrupts the flow of the reading. For example:

"It comes from studies of hormonal responses in normal and malignant osteoblasts (Luben and Cohn, 1976; Martin *et al.* 1976; Partridge *et al.*, 1981) and from direct demonstration of specific binding by autoradiography to osteoblasts in vitro (Silve *et al.*, 1982; Evely *et al.*, 1991) and in vivo (Rouleau *et al.*, 1986)."[2]

A suggestion would be to make use of superscripts and numbers at the end of the each chapter.

In comparison to other resources, *Osteoporosis* is a highly specialized book aimed at those who are involved in the study of metabolic bone diseases. Due to this specialized approach, relevant clinical points get lost in the deluge of minutiae and citations from various studies. The degree of specialization is similar to that found in *Osteoporosis: Diagnostic and Therapeutic Principles.*[3] In *Osteoporosis: A Clinical Guide*,[4] the clinical points are more delineated and there is less emphasis on providing an exhaustive review of the disease.

Given the highly specialized knowledge found within this book, the cost of the book is a relatively fair price. However, I would not recommend purchasing this book unless you have a particularly keen interest in osteoporosis and/or are studying in this highly specialized field. Although *Osteoporosis* is not meant to serve as a primary text, it can be useful as an additional reference book for medical students, residents and practicing physicians who are interested in knowing more about particular aspects of osteoporosis.

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3. Rosen CJ, ed. *Osteoporosis: Diagnostic and Therapeutic Principles.* Totowa: Humana Press Inc., 1996.
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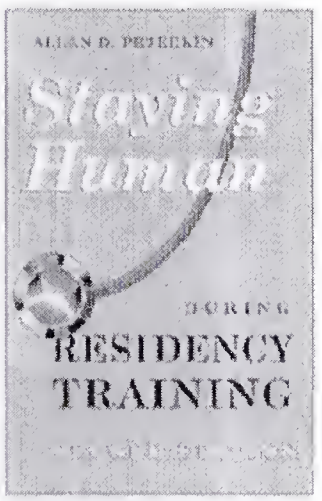

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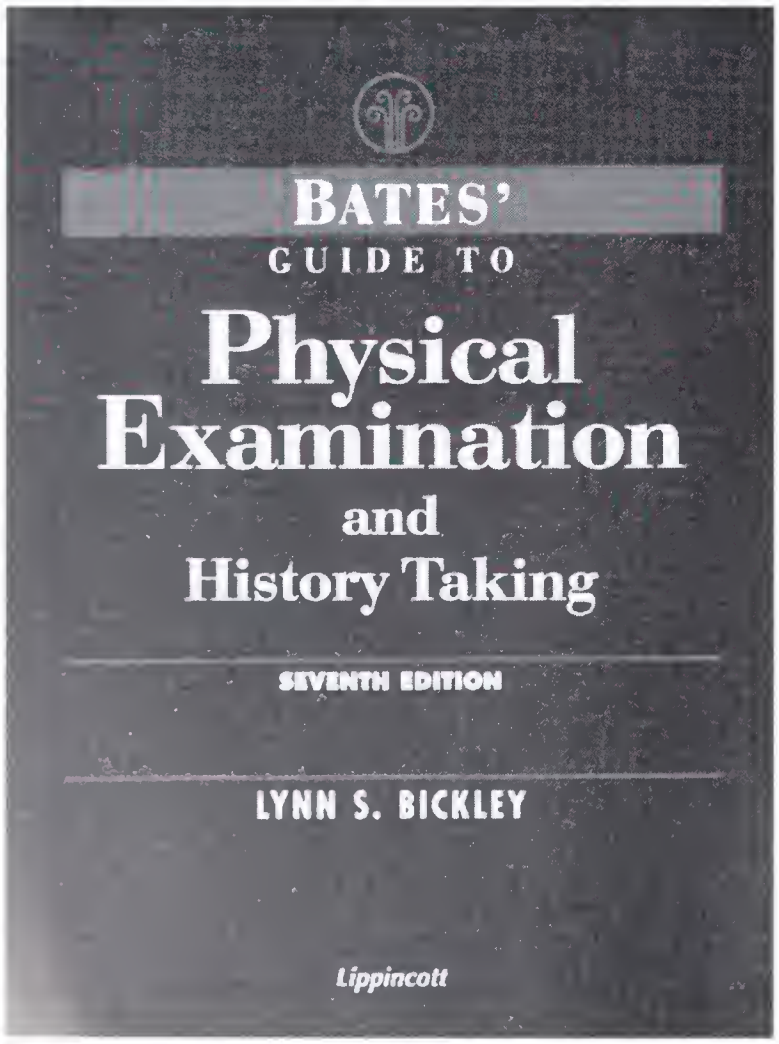
UTMJ Reviews – The Essentials

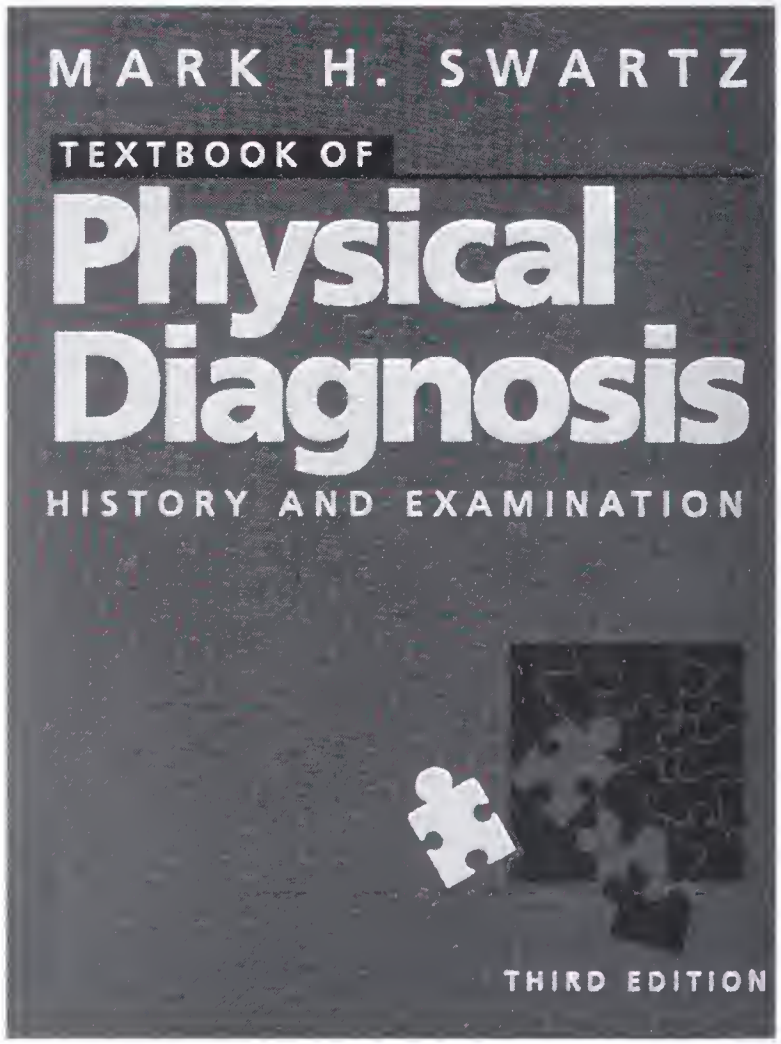
Reviewed by Stephanie Wiesenthal, B.Sc., M.Sc. (OT2) and Amy S. M. Tam, B.Sc. (OT2)

"The Essentials" is a new series of book reviews intended for textbooks dealing with essential subjects in undergraduate medical education such as human physiology, pharmacology and anatomy. Two books covering the same topic will be reviewed in each issue of the *UTMJ* to provide a good comparison for readers. This issue's topic is history taking and physical examination.

Bates' Guide to Physical Examination and History Taking, 7th ed.
Editors: Lynn S. Bickley and Robert A. Hoekelman
Publisher: Lippincott
Date of Publication: 1999
Number of pages: 789 pages
Cost: Hardcover edition, $92.95 (CDN)

Textbook of Physical Diagnosis, History and Examination, 3rd ed.
Editors: Mark H. Swartz
Publisher: W.B. Saunders Company
Date of Publication: 1998
Number of pages: 720 pages
Cost: Hardcover edition, $84.92 (CDN)





There is no equal to the privileges physicians have in sharing the personal lives of their patients and being able to physically examine them. The skills required for empathetic interviewing that elicits all of the necessary information take years to develop as does learning physical examination techniques. Many texts and pocket references have been written on these subjects for new medical students. Both *Bates' Guide to Physical Examination* and *History Taking and Textbook of Physical Diagnosis, History and Examination* offer thorough introductions to both topics.

Bates' Guide to Physical Examination and History Taking is a practical, well written, and informative guide to the art and practice of physical examination. Along with a complete description of physical manoeuvres, Bickley and Hoekelman provide a helpful guideline to taking a complete history. What is most impressive is the discussion regarding potentially sensitive issues such as religious and cultural differences, drug use, psychiatric illnesses and alcoholism. The text addresses the situations that might pose a challenge for the medical student and does so without being condescending to the reader.

In addition, *Bates' Guide to Physical Examination and History Taking* provides a thorough review of symptoms and excellent examples of questions which could be inquired of the patient. This section is complemented by well-organized and comprehensive tables outlining differential diagnoses for common symptoms such as headaches, vertigo, and chest pain.

Bickley and Hoekelman assume some prior knowledge of medicine and anatomy, but the text is supplemented throughout by further explanations for symptoms mentioned in its margins. Instructions are accompanied by clear and beautifully illustrated diagrams such that the reader can readily understand the task asked of them. In general, the illustrations are excellent and of superior quality.

On the downside, students may feel overwhelmed by the volume of information found in the book. A suggestion to the authors would be to include an overall outline of the physical examination manoeuvres before beginning the in depth discussion. Overall *Bates' Guide to Physical Examination and History Taking* is an excellent and informative book. It is highly recommended for medical students of all years.

The *Textbook of Physical Diagnosis, History and Examination* is a concisely written text that contains all of the information necessary for a student to begin learning about clinical aspects of medicine. It is a good reference for those wishing to quickly review the appropriate questions and physical examination manoeuvres before class. The figures are above average, but there are occasional black and white line illustrations that need colour to make subtle clinical signs stand out. The inclusion of vocabulary sections in each chapter should be part of every textbook of physical diagnosis. However, the presentation of information makes it difficult for readers to learn clinical reasoning skills. Explanations of interview questions are included separately from the questions, leaving the beginner wondering about topics that seem unrelated. Tables, which would help students differentiate similarly presenting diseases, could be used more often.

Unfortunately, the text begins with a weak introduction to interviewing. While the first chapter on interviewing tactics serves as a nice framework for the medical history, the next on patient responses divides patients into limited categories and tries to provide one-phrase solutions to dealing with them. A well-intended chapter on cultural considerations makes poor use of figures and is neither well researched nor comprehensive. Most of the figures in this chapter are of no value. Readers will have to look elsewhere for illustrations that can be used to identify complementary remedies and listings of the currently known drug-herbal interactions. A section on Native Americans only discusses alcohol abuse and domestic violence, neglecting to mention other important facts such as the endemic nature of diabetes mellitus type 2 amongst these peoples. The fourth chapter of this section, a mock interview, fails to show the importance of socioeconomic factors, and, in fact, teaches students precisely how to avoid cues that social support and financial burdens may be impediments. This theme of medicine before the patient continues throughout the text, with much needed advice on examining women and discussing sensitive information with patients being absent or reduced to single sentences. Suggested questions for history taking, while comprehensive, often include medical jargon and sound detached.

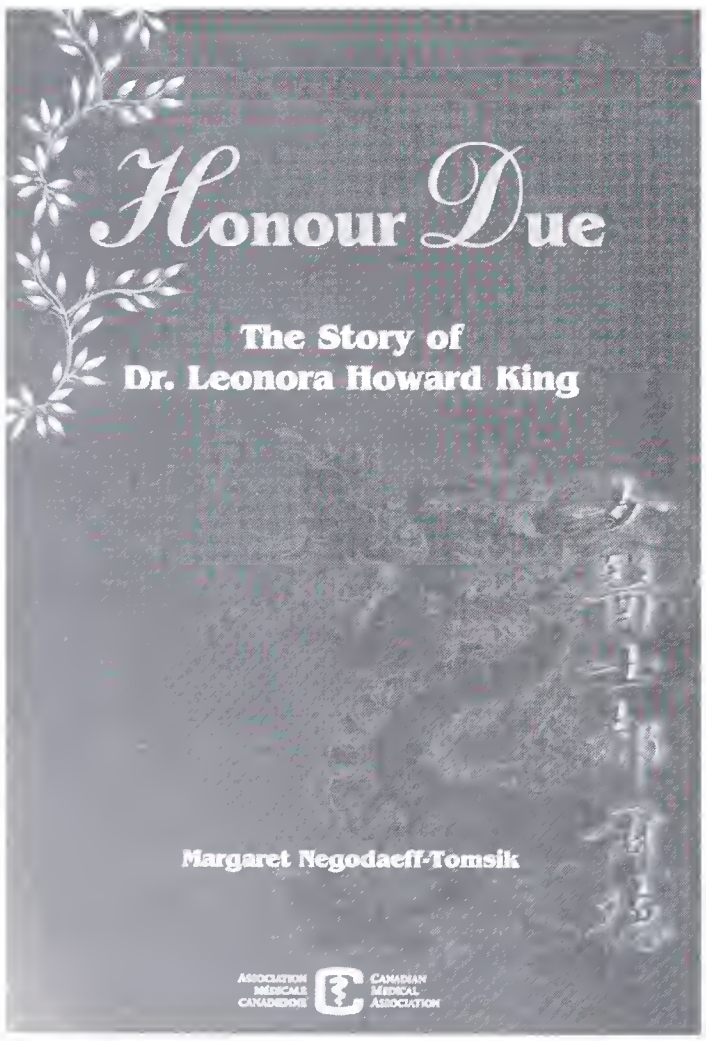
Textbook of Physical Diagnosis, History and Examination has many of the elements needed to make a good text, such as clear and concise descriptions of signs and symptoms, but falls short of teaching students a well-rounded approach to patient care.

UTMJ Reviews – History of Medicine

Honour due: The Story of Dr. Leonora Howard King

Reviewed by Michael Klompas, B.Sc. (OTO)

Editors: Margaret Negodaeff-Tomsik
Publisher: Canadian Medical Association
Date of Publication: 1999
Number of Pages: 236
Cost: Paperback edition, $24.95 (CDN)



Caduceus and the Dragon

Honour Due: The Story of Dr. Leonora Howard King takes as its subject the tense meeting of Western missionaries and indigenous Chinese at the turn of the century. Motivated by the lure of adventure and paternalistic pity for the "naive heathens" of distant lands, many idealistic young Christians headed East under the sponsorship of Western missionary societies. Unfortunately, their self-righteous efforts to enlighten native Chinese were often met with disdain at best, and ridicule or violence not infrequently. Moreover, the small cohort of Chinese who were prepared to attend missionary lectures seemed more interested in the soup served than in learning about the Christian saviour. Perhaps somewhat cynically, a medical degree was consequently considered an invaluable asset for proselytisation. While provision of medical services was consistent with Christian notions of charity it also allowed missionaries better access to the masses they hoped to convert during vulnerable moments in their lives.

One of the most remarkable physician-missionaries to enter the Middle Kingdom was the Canadian born Dr. Leonora Howard King. Although raised on a farm in Ontario she was forced to seek medical training at the University of Michigan after being denied entry to

Canadian medical schools on account of her gender. In her last year of training, she was recruited by the Woman's Foreign Missionary Society for work in China. Over the course of the next forty-seven years, she had a profound impact upon countless Chinese women and children. She had the good fortune to win the respect of a highly placed Chinese official after successfully treating his wife. Dr. Howard King henceforth enjoyed this official's powerful patronage as both benefactor for her medical work and protector for her person during periods of tremendous anti-Western hostility and savage violence.

With the help of her patron she was able to open a number of free clinics for women and children, found a hospital, and establish a medical school to train female physicians. She is also rumoured to have helped sway China's diplomatic relations with the West. The story goes that when the former President of her medical school was appointed American Minister to the Court of Peking (Beijing), she vouched for his credibility via her patron on the basis of the Minister's role in assuring her own medical training. The Chinese court honoured Dr. Howard King for her contributions by making her the first Western woman to be elevated to the level of mandarin, a citation akin to knighthood.

Unfortunately, the author of *Honour Due* had the unenviable task of reconstructing Dr. King's life almost entirely from the accounts of contemporaries rather than from personal letters or diaries. The greatest frustration in reading this book is the absence of Dr. Howard King's own thoughts and observations upon the vivid personalities and events that surrounded her. Instead, Leonora's biography reads more like a generalised history of the Western missionary effort in China rather than a person-specific biography. The author attempts to make up for the lack of personal details with speculation upon what Dr. Howard King might have seen or thought. To the author's credit, her efforts are often richly evocative. Here is her surmised description of Dr. Howard King's initial entry into the city that would become her home:

> In any season, the million residents of this thriving port sloshed through a quagmire of indescribable stench, the mud augmented every few metres by water carriers on their way to and from the great broad river of the stinking Grand Canal. Lanky yellow dogs covered in open sores skulked in alleyways just big enough for a donkey to pass through, snarling at each other over the bursting carcass of a rat that had recently made the long voyage from Singapore.

In all, *Honour Due* is a fascinating account of a remarkable period of history. It deserves to be read by anyone interested in the intersection of faith, healing, and Western imperialism.

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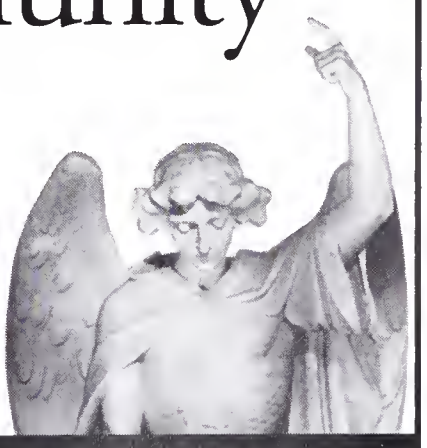

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e-mail: editors.utmj@utoronto.ca website: www.utmj.org

The deadlines for submissions for the 77th edition of the *UTMJ* are: October 1, 1999; January 14, 2000; and April 3, 2000.

The paper should be submitted by an author, preferably the principal author, who should indicate in a covering letter:

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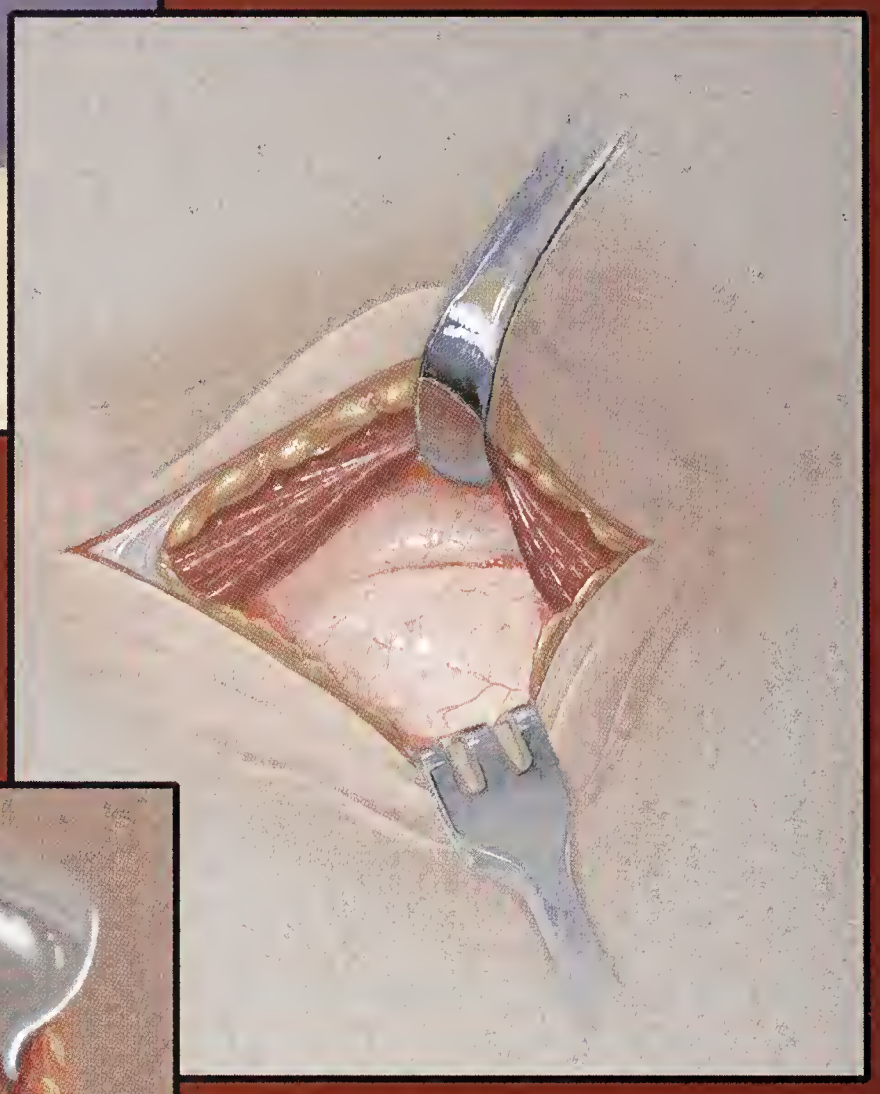

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